

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 239/46, 403/04, 403/06, 403/14, 401/04, 401/06, 413/14, A61K 31/505		A1	(11) International Publication Number: WO 99/02501
			(43) International Publication Date: 21 January 1999 (21.01.99)
(21) International Application Number: PCT/SE98/01240		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 25 June 1998 (25.06.98)			
(30) Priority Data: 9702651-2 9 July 1997 (09.07.97) SE			
(71) Applicant (for all designated States except US): ASTRA PHARMACEUTICALS LTD. [GB/GB]; Home Park, Kings Langley, Herts WD4 8DH (GB).			
(71) Applicant (for MG only): ASTRA AKTIEBOLAG (publ) [SE/SE]; S-151 85 Södertälje (SE).		Published With international search report.	
(72) Inventors; and (75) Inventors/Applicants (for US only): KINDON, Nicholas [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics LE11 5RH (GB). MEGHANI, Premji [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics LE11 5RH (GB). THOM, Stephen [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics LE11 5RH (GB).			
(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).			
(54) Title: NOVEL COMPOUNDS			
(57) Abstract The invention relates to new pharmaceutically active compounds (I) which are P2-purinoceptor 7-transmembrane (TM) G-protein coupled receptor antagonists, compositions containing them and processes for their preparation, in which R ² is a group of formula (ii) or (iii).			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

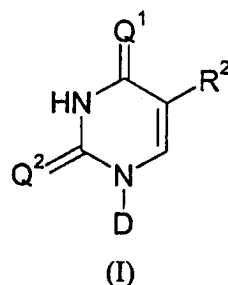
NOVEL COMPOUNDS

The invention provides new pharmaceutically active compounds, compositions containing them and processes for their preparation. The compounds are useful in therapy because
5 they are P2-purinoceptor 7-transmembrane (TM) G-protein coupled receptor antagonists.

ATP receptors have been shown to be present on a wide number of different cell types (Dubyak *et al* Am J Physiol (1993) 265, C577-C606). Neutrophils, monocytes and macrophages have been isolated from several species including humans and ATP and/or
10 UTP have been shown to increase intracellular calcium levels. Activation of these receptors on leukocytes can either directly stimulate certain types of inflammatory response or can prime the effector cells to other inflammatory mediators *in vivo*. ATP can upregulate the expression of adhesion molecules (Freyer *et al* J Immun. (1988) 141, 580-586) which causes enhanced adhesion of circulating leukocytes to endothelial cells and
15 their enhanced migration into the tissue space. ATP has also been shown to promote chemotaxis of both neutrophils and eosinophils (Verghese *et al* J. B. C. (1996) 271, 15597-15601 and Burders *et al* Blood (1993) 81, 49-55) which may promote an inflammatory response. ATP priming of neutrophils can also potentiate superoxide production (Seifert *et al* Eur J Biochem (1989) 181, 277-285). ATP receptors are also present on a number of
20 other cell types such as chondrocytes, keratinocytes, microglia and goblet cells (Leong *et al* BBA (1994) 1201, 298-304; Pillai *et al* J Clin Invest (1992) 90, 42-51; Walz *et al* J Neuroscience (1993) 13, 4403-4411 and Abdullah *et al* Biochem J (1996) 316, 943-951). Stimulation of the receptors on these cells can stimulate or enhance inflammatory responses and antagonist of the receptor may therefore be of use in a number of
25 inflammatory diseases such as asthma, inflammatory bowel disease, ARDS, psoriasis, rheumatoid arthritis, myocardial ischaemia, COPD, cystic fibrosis, atherosclerosis, restenosis, periodontal disease, septic shock, osteoarthritis and stroke. ATP receptors have also been reported on tumour cells (Dubyak *et al* J. Biol. Chem., (1985) 260, 10653 - 10661 and Wagner *et al* Gastroenterology, (1997), 112(4) suppl. page A1198) and may be
30 involved in the development of cancer. Antagonists may therefore be useful in treatment of cancer.

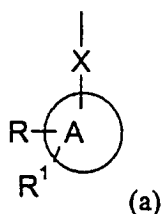
According to the invention there is provided a compound of formula (I) or salts thereof:

2



in which:

- 5 D is hydrogen, C₁₋₆alkyl or a group of formula (a):

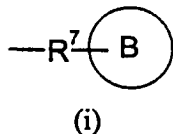


- 10 where A is a 6-membered heterocyclic ring containing 1 to 3 nitrogen atoms or a fused 5,6-bicyclic ring containing 1 to 4 nitrogen atoms;

X is a bond or CH₂ group;

R is hydrogen, NO₂, NH₂, N(C₁₋₆alkyl)₂, CO₂H, CO₂C₁₋₆alkyl, phenyl substituted by CH₂CO₂H, or CONR³R⁴ where R³ and R⁴ are independently hydrogen, C₁₋₆alkyl optionally substituted by hydroxy and/or optionally interrupted by oxygen, nitrogen or sulfur;

- 15 R¹ is -R⁵-tetrazol-5-yl where R⁵ is a bond, OCH₂, SCH₂, CONH, CONHCH₂, CONHCH₂CONH, NHCH₂CONH, NHCH(R³) or -R⁵-CO₂H where R⁵ is a bond, OCH₂, SCH₂, CONHCH₂ or NHCH(R³) where R³ is as defined above or R⁵ is NR⁶(CH₂)_q where R⁶ is hydrogen or C₁₋₆alkyl and q is 1 or 2, or R¹ is a group of formula (i):

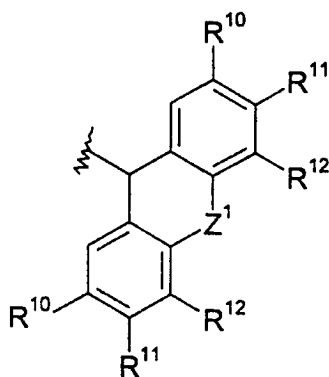


- 20 where B is a 4-, 5-, or 6-membered saturated ring containing a nitrogen atom optionally substituted by hydroxy and substituted by CO₂H or CONH-Het where Het is tetrazol-5-yl,
 25 or a thiazole or thiadiazole ring substituted by CH₂CO₂H, or B is a 5-membered aromatic heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur

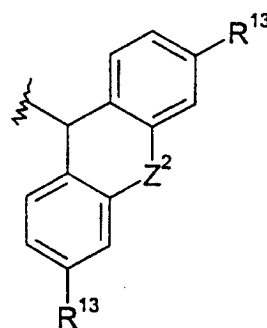
optionally substituted by CF_3 , CO_2H , $\text{CH}_2\text{CO}_2\text{H}$, $\text{C}(\text{CO}_2\text{H})=\text{N}-\text{OMe}$, tetrazol-5-yl or CH_2 tetrazol-5-yl; and

R^7 is a bond, sulfur atom, a group $-\text{NR}^8-\text{CH}(\text{CO}_2\text{H})-\text{CH}_2-$, or a group $-\text{CONR}^8(\text{CH}_2)_p\text{CONR}^9-$ or $-\text{NR}^8-(\text{CH}_2)_p\text{CONR}^9-$ where R^8 and R^9 are independently hydrogen or C_{1-6} alkyl and p is 1 or 2;

R^2 is a group of formula (ii) or (iii):



(ii)



(iii)

where R^{10} groups are independently hydrogen, halogen, methoxy, methylthio or C_{1-2} alkyl (optionally substituted by one or more fluorine atoms);

R^{11} groups are independently hydrogen, halogen, hydroxy, C_{1-3} alkylthio, C_{1-4} alkyl (optionally substituted by one or more fluorine atoms), C_{3-4} cycloalkyl, MeOCH_2 , MeSCH_2 or C_{1-2} alkoxy;

R^{12} groups are independently hydrogen, halogen or methyl (optionally substituted by one or more fluorine atoms);

Z^1 is $\text{CH}=\text{CH}$, $\text{CF}=\text{CH}$ or $\text{CF}=\text{CF}$;

Z^2 is a single bond, oxygen, sulphur, $\text{CH}_2\text{CH}=\text{CH}$, $\text{CH}_2\text{CH}=\text{CHCH}_2$ or a C_{1-4} alkylene group optionally interrupted by an oxygen or sulphur atom;

R^{13} are independently hydrogen, halogen, C_{1-2} alkyl, CF_3 or a methylthio group or hydroxy;

Q^1 and Q^2 each independently represent an O or S;

provided that when Q^1 is oxygen, R^2 is a group of formula (ii).

Alkyl groups, whether alone or as part of another group, can be straight chain or branched. Unless stated otherwise, the term alkyl as used herein refers to C_{1-6} alkyl groups, such as methyl, ethyl, propyl and butyl groups.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be
5 separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

Suitably D is hydrogen, C₁₋₆alkyl or a group of formula (a) as defined above. When D is
10 C₁₋₆alkyl, preferred alkyl groups include methyl.

Preferably D is a group of formula (a) where A is a 6-membered heterocyclic ring containing 1 or 2 nitrogen atoms or a fused 5,6-bicyclic ring containing 4 nitrogen atoms. Examples of suitable 6-membered heterocyclic rings include pyridine and pyrimidine
15 rings. More preferably A is pyrimidine. Preferably R and R¹ are meta or para with respect to the uracil group.

Suitably X is a bond or CH₂ group. Preferably X is CH₂ when A is pyridine and X is a bond when A is pyrimidine.

Suitably R is hydrogen, NO₂, NH₂, N(C₁₋₆alkyl)₂, CO₂H, CO₂C₁₋₆alkyl, phenyl substituted by CH₂CO₂H, or CONR³R⁴ where R³ and R⁴ are independently hydrogen, C₁₋₆alkyl optionally substituted by hydroxy and optionally interrupted by oxygen, nitrogen or sulfur. Preferably R is hydrogen.

Suitably R¹ is -R⁵-tetrazol-5-yl where R⁵ is a bond, OCH₂, SCH₂, CONH, CONHCH₂, CONHCH₂CONH, NHCH₂CONH, NHCH(R³) or -R⁵-CO₂H where R⁵ is a bond, OCH₂, SCH₂, CONHCH₂ or NHCH(R³) where R³ is as defined above or R⁵ is NR⁶(CH₂)_q where R⁶ is hydrogen or C₁₋₆alkyl and q is 1 or 2, or R¹ is a group of formula (i) as defined above.

When R¹ is -R⁵-CO₂H, R⁵ is preferably SCH₂, NHCH₂ or NMeCH₂. When R¹ is a group of
30 formula (i) then R⁷ is preferably a bond when B is a 4-, 5- or 6-membered saturated ring containing a nitrogen atom substituted by CO₂H and optionally substituted by hydroxy.

When B is a 5-membered aromatic heterocycle then R⁷ is preferably a group

35 -CONR⁸(CH₂)_pCONR⁹- or -NR⁸-(CH₂)_pCONR⁹- particularly such a group where R⁸ is hydrogen or methyl and R⁹ is hydrogen and p is 1. Preferred rings B include substituted

thiazole and thiadiazole substituted by CO₂H or CH₂CO₂H, more preferably substituted by CH₂CO₂H.

Suitably R² is a group of formula (ii) or (iii). Preferably R² is a group of formula (ii) where
 5 Z¹ is CH=CH. Suitably R¹¹ groups are independently hydrogen, halogen, hydroxy, C₁₋₃ alkylthio, C₁₋₄ alkyl (optionally substituted by one or more fluorine atoms), C₃₋₄ cycloalkyl, MeOCH₂, MeSCH₂ or C₁₋₂ alkoxy. Preferably both R¹¹ groups are hydrogen or methyl or one is methyl and the other is ethyl or propyl. Preferably R¹⁰ and R¹² are both hydrogen.

10 Suitably Q¹ and Q² each independently represent an O or S. Preferably Q¹ is S or O and Q² is O.

Particularly preferred compounds of the invention include:

- 15 6-[[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]methyl]-2-pyridinecarboxylic acid
 2-[[6-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyridazin-3-yl]thio]acetic acid
 5-[5*H*-Dibenzo[*a,d*]cyclohepten-5-yl]-1-[6-[[5-(trifluoromethyl)-1,2,4-triazol-3-yl]thio]pyridazin-3-yl]-2,4(1*H*,3*H*)-pyrimidinedione
 20 5-[5*H*-Dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-4-thioxo-1-[6-[[5-(trifluoromethyl)-1,2,4-triazol-3-yl]thio]pyridazin-3-yl]-2(1*H*)-pyrimidinone
 4-[2-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]-4-[carboxymethylthio]pyrimidin-5-yl]phenylacetic acid
 25 2-[[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]thio]acetic acid
N-[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine
N-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine
 30 *N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine
 2-[2-[[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid
 35 *N*-[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline

N-[4-[-5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline

(2*S-trans*)-*N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-4-hydroxy-2-pyrrolidinecarboxylic acid

5 *N*^α-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-histidine

(±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid

10 2-[2-[[2-[Dimethylamino]-4-[5-{2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-6-yl]amino]acetyl]amino]-4-thiazoleacetic acid

N-[2-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-5-[methoxycarbonyl]pyrimidin-4-yl]glycine

15 4-[[Carboxymethyl]amino]-2-[5-{2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-5-pyrimidinecarboxylic acid

(±)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*N*-methylglycine

20 (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid

2-[2-[[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid

25 (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid

(±)-2-[2-[[4-[3,4-Dihydro-5-{2-methoxy-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid

30 (±)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-3-azetidinecarboxylic acid

2-[2-[[6-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-4-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid

(±)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline

35 (±)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline

(±)-2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-9*H*-purine-9-acetic acid.

N-[2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-5-nitropyrimidin-4-yl]glycine.

5 (±)-2-[2-[[4-[3,4-dihydro-5-{2-methyl-8-[1-methylethyl]-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid

(±)-2-[2-[[4-[3,4-Dihydro-5-{2-methyl-8-propyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid

(±)-*N*-[4-[3,4-Dihydro-5-{2-methyl-8-propyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2-oxo-4-thio-10
thio-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*N*-methylglycine

(±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-5-thiazoleacetic acid

(±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazolecarboxylic
15 acid.

(±)-2-[[1-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]azetidin-3-yl]carbonylamino]-4-thiazoleacetic
acid

20 (±)-2-[2-[[4-[3,4-Dihydro-5-{2-hydroxy-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid.

(±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-α-[methoxyimino]-4-thiazoleacetic acid

25 (±)-*N*-[(1*H*)-Tetrazol-5-yl]-1-[4-[5-{2-ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-3-azetidinecarboxamide

(±)-2-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino-*N*-[4-[1*H*-tetrazol-5-ylmethyl]thiazol-2-yl]acetamide

30 (±)[[5-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-3-(1,2,4-thiadiazole)]acetic acid

(±)2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-4-pyrimidinecarboxylic acid

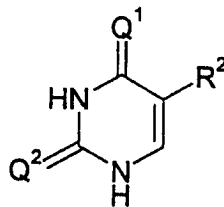
(±)*N*-[[[2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-4-yl]carbonyl]glycine
35

- (±)2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-*N*-[(1*H*)-tetrazol-5-yl]-4-pyrimidinecarboxamide
- (±)2-[[6-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyridazin-3-yl]thio]acetic acid
- 5 (±)2-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]-*N*-[(1*H*)-tetrazol-5-yl]acetamide
- (±)*N*-[4-[5-{2-Ethyl-8-hydroxy-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-3-azetidinecarboxylic acid
- (±)2-[[[4-[5-{2-Ethyl-8-hydroxy-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid
- 10 (±)2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-*N*-[{(1*H*)-tetrazol-5-ylamino}carboxymethyl]-4-pyrimidinecarboxamide
- (±)4-[Carboxymethylamino]-2-[5-[2-ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-2*H*-pyrimidin-1-yl]-5-pyrimidinecarboxylic acid
- 15 5-[2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidine
- 5-[2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-1-methyl-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidine
- 20 and salts thereof.

In a further aspect the invention provides a process for the preparation of a compound of formula (I) which comprises:

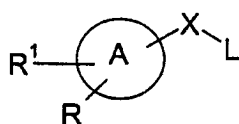
(a) reacting a compound of formula (II):

25



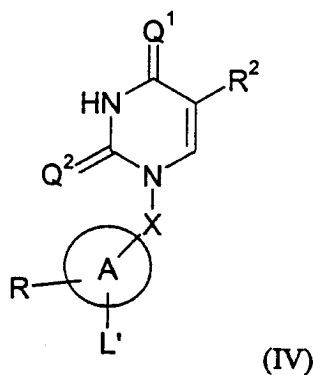
(II)

- 30 where Q^1 and Q^2 are as defined in formula (I) and R^2 is as defined in formula (I) or is a protected derivative thereof with a compound of formula (III):



(III)

- 5 where R, R¹ and A are as defined in formula (I) or are protected derivatives thereof, X is as defined in formula (I) and L is a leaving group, or
 (b) reacting a compound of formula (IV):

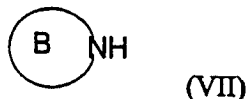
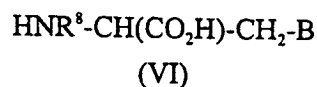
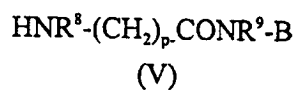


(IV)

10

where Q¹, Q², R² and X are as defined in formula (I), R and A are as defined in formula (I) or are protected derivatives thereof and L¹ is a leaving group with a compound of formula (V), (VI) or (VII):

15



(VII)

- 20 where R⁸, R⁹ and p are as defined in formula (I) and B is as defined in formula (I) or is a protected derivative thereof, or
 (c) when R¹ is a group -R⁵-CO₂H and R⁵ is SCH₂ or NR⁶(CH₂)_q, reacting a compound of formula (iv) as defined above with a compound H-R⁵-CO₂R¹⁴ where R⁵ is SCH₂ or NR⁶(CH₂)_q and R¹⁴ is an ester forming group;
 25 and optionally thereafter (a), (b) or (c) in any order:
- removing any protecting groups

- converting the compound of formula (I) into a further compound of formula (I)
- forming a salt

Reaction of compounds of formulae (II) and (III) can be carried out in the presence of a
5 suitable base, for example a metal carbonate such as potassium carbonate or cesium
carbonate in a suitable polar solvent such as NMP, dimethylformamide or
dimethylsulphoxide at ambient or elevated temperature, for example at about 80°C.
Preferably L is halogen when X is a bond, in particular chloro or fluoro. When X is CH₂, L
is preferably chloro. Alternatively for compounds where X is CH₂, the compound of
10 formula (II) can be silylated with a suitable silylating reagent such as a trialkylsilylchloride
and/or 1,1,1,3,3,3-hexamethyldisilazane in a suitable solvent such as pyridine, toluene or
1,4-dioxane at a temperature of about 80°C to about 140°C followed by addition of the
compound of formula (III) in a suitable solvent such as acetonitrile at elevated temperature,
for example at reflux. We prefer to silylate using bis(trimethylsilyl)trifluoroacetamide in
15 refluxing 1,2-dichloroethane followed by treatment the appropriate compound of formula
(III) (where L is halogen, preferably bromide or chloride) in acetonitrile and 1,2-
dichloroethane at reflux.

Compounds of formula (IV) can be reacted with compounds H-R⁵-CO₂H in the presence of
20 a suitable base. When R⁵ is SCH₂, the base is preferably NaH and when R⁵ is NR⁶(CH₂)_q
the base is preferably an organic amine such as di-isopropylethylamine. The group R¹⁴ is a
suitable ester forming group such as benzyl or C₁₋₆ alkyl. Compounds of formula (IV) can
also be reacted with compounds of formulae (V), (VI) or (VII) using the procedure
described above for when R⁵ is NR⁶(CH₂)_q.

25

It will be appreciated by those skilled in the art that in the process described above the
functional groups of intermediate compounds may need to be protected by protecting
groups.

30 Functional groups which it is desirable to protect include hydroxy, amino and carboxylic
acid. Suitable protecting groups for hydroxy include organosilyl groups (e.g.
tert-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), benzyl and tetrahydro-
pyranyl. Suitable protecting groups for amino include *tert*-butoxycarbonyl or benzyloxy
carbonyl. Suitable protecting groups for carboxylic acid include C₁₋₆ alkyl or benzyl esters.
35 The protection and deprotection of functional groups may take place before or after a
reaction step.

The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T. W. Greene & P. G. M. Wutz, Wiley-Interscience
5 (1991).

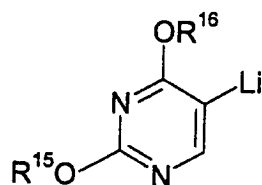
In particular compounds of formula (III) where R¹ contains a carboxylic acid group can be protected as esters, particularly as C₁₋₆alkyl esters. Basic hydrolysis of such esters can be performed using metal hydroxides or quaternary ammonium hydroxides such as sodium
10 hydroxide in a solvent such as an aqueous alcohol, 1,4-dioxane, tetrahydrofuran or dimethylformamide at a temperature between 10°C and 100°C. When Q¹/Q² are oxygen, acidic hydrolysis may also be performed using mineral acid such as HCl or a strong organic acid such as trifluoroacetic acid in a suitable solvent such as 1,4-dioxane. We prefer basic hydrolysis using lithium hydroxide in aqueous tetrahydrofuran or aqueous
15 methanol at ambient temperature.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures, for example using known alkylation, hydrolysis, esterification and amide formation chemistry. Compounds of formula (I) where Q¹ is oxygen can be
20 converted to a corresponding compound of formula (I) where Q¹ is sulfur using standard thiation conditions for conversion of uridine and thymidine nucleosides in their corresponding thio-nucleoside derivatives (see "Chemistry of Nucleosides and Nucleotides" edited by Leroy B. Townsend, Plenum Press volume 1). Thiation may be achieved using reagents such as diphosphorus pentasulphide or Lawesson's reagent in a
25 solvent such as pyridine, 1,4-dioxane, toluene, xylene, or tetrahydrofuran at a temperature of about 50°C to about 130°C. We prefer to use Lawesson's reagent in 1,4-dioxane at about 100°C when selectivity can be achieved.

Thiation can also be achieved by displacement of a suitable leaving group in the 2- or 4-
30 position of the uracil by hydrogen sulphide in a suitable solvent such as pyridine and triethylamine at ambient temperature. Suitable leaving groups include alkylthio or halogen, preferably alkylthio, more preferably methylthio.

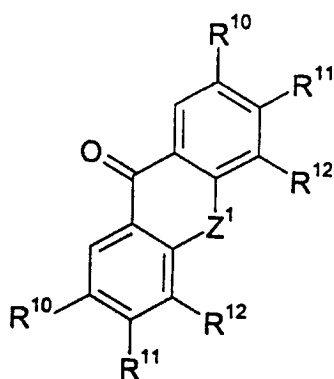
Compounds of formula (II) where Q¹ and Q² are oxygen can be prepared by reaction of a
35 compound of formula (VIII):

12

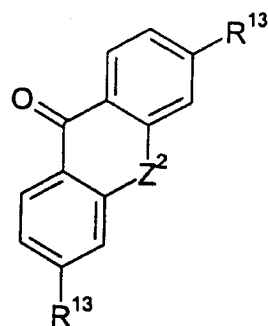


(VIII)

- 5 where R^{15} and R^{16} are independently C_{1-6} alkyl or benzyl with a compound of formula (IX) or (X):



(IX)



(X)

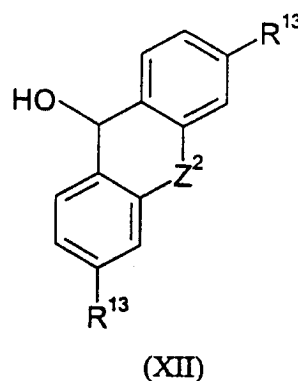
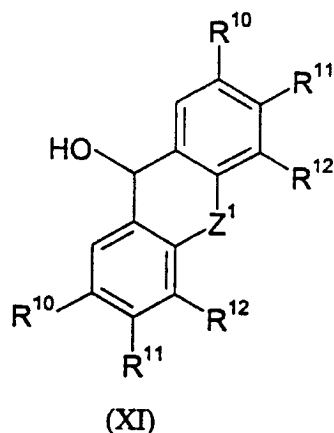
- 10 where Z^1 , Z^2 , R^{10} , R^{11} , R^{12} and R^{13} groups are as defined in formula (I) followed by reduction of the resulting alcohol. Compounds of formula (VIII) are prepared by treating the corresponding halide with an alkyl lithium reagent (alkyl=n-Butyl, sec-Butyl, tert-Butyl) in solvents such as tetrahydrofuran or diethyl ether at low temperature e.g. -40°C to -78°C .

- 20 The resulting alcohol can then be reduced to compounds of type (II) by treatment with a trialkylsilane such as triethylsilane in a suitable solvent such as dichloromethane, chloroform, or 1,2-dichloroethane and an acid or Lewis acid such as trifluoroacetic acid or borontrifluoride diethyl ether complex. We preferred to perform the metal halogen exchange on 5-bromo-2,4-bis(1,1-dimethylethoxy)pyrimidine using n-butyl lithium at about -78°C in tetrahydrofuran.

- 25 When the lithio species is quenched with a substituted 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one the resulting substituted 5-(2,4-bis(alkoxy)pyrimidin-5-yl)-

10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol can then be converted to the uracil of formula (II) (where Z^1 is $\text{CH}=\text{CH}$) by refluxing in a carboxylic acid solvent (D. Hellwinkel and T. Becker, Chem. Ber., 1989, 122, 1595). Preferred acids include acetic acid. In some cases further treatment with trifluoroacetic acid at reflux may be required for the dehydration to give the substituted uracil (II).

Compounds of formula (II) can also be prepared from uracil and the appropriately substituted alcohols of formula (XI) and (XII):



in which Z^1 , Z^2 , R^{10} , R^{11} , R^{12} and R^{13} groups are as defined in formula (I) by refluxing in a carboxylic acid solvent such as acetic acid (J.O.C., 1974, 39, 587).

Salts of the compounds of formula (I) may be formed by reacting the free acid, or a salt thereof, with one or more equivalents of the appropriate base (for example ammonium hydroxide optionally substituted by C_{1-6} -alkyl or an alkali metal or alkaline earth metal hydroxide). The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. water, alcohol or acetone, which may be removed *in vacuo*, or by freeze drying. The reaction may also be a metathetical process or it may preferably be carried out on an ion exchange resin. The non-toxic pharmaceutically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

Novel intermediates form a further aspect of the invention.

The compounds of the invention have been submitted to the assay outlined below and have

been found to be P2 7-TM G-protein receptor antagonists, particularly to the P2Y2 receptor. Accordingly they are useful in therapy and are, in particular, indicated for use as anti-inflammatory agents useful in a number of inflammatory diseases such as asthma, inflammatory bowel disease, ARDS, psoriasis, rheumatoid arthritis, myocardial ischaemia, COPD, cystic fibrosis, artherosclerosis, restenosis, peridontal disease, septic shock, osteoarthritis and stroke. The compounds of the invention can be co-administered with other anti-inflammatory agents. ATP receptors have also been reported on tumour cells and may be involved in the development of cancer. Antagonists may therefore be useful in treatment of cancer.

10

The invention provides in a further aspect a method of treating an inflammatory condition which comprises administering to a patient in need of therapy, a therapeutically effective amount of a compound of the invention.

15 According to the invention there is further provided use of the compounds of the invention in the manufacture of a medicament for use in the treatment of an inflammatory condition.

The compounds may be administered orally, topically e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA areosols and dry powder formulations, e.g. Turbuhaler® formulations or by parenteral administration in the form of sterile parenteral solutions or suspensions.

25 The invention further provides a pharmaceutical composition comprising a compound according to the present invention in association with a pharmaceutically acceptable excipient and/or adjuvant. Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction. For example a chelating or sequestering agent, an antioxidant, a tonicity adjusting agent, a pH modifying agent and/or a buffering agent are suitable additives.

30 The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

35 A pharmaceutical composition according to the present invention could optionally be prepared in freeze dried form using any lyophilisation techniques commonly used within the pharmaceutical area. Upon use but before administration, such pharmaceutical

compositions are generally reconstituted in a pharmaceutically acceptable excipient. Preferably a solution of the pharmaceutical composition according to the invention obtained after reconstitution is an isotonic solution. Such a pharmaceutical composition according to the present invention when reconstituted is preferably administered by
5 injection, for example intravenously, subcutaneously or intramuscularly.

In the examples the NMR spectra were measured on a Varian Unity Inova 300 or 400 MHz spectrometer and the MS spectra measured as follows: EI spectra were obtained on a VG 70-250S or Finnigan Mat Incos-XL spectrometer, ESI and APCI spectra were obtained on
10 Finnigan Mat SSQ7000 or a Micromass Platform spectrometer. Where necessary, the reactions were performed under an inert atmosphere of either nitrogen or argon. Where necessary, preparative HPLC separations were generally performed using a Novapak[®], Bondapak[®], or Hypersil[®] column packed with BDSC-18 reverse phase silica gel. Chromatography was generally performed using Matrex Silica 60[®] (35-70 micron) or
15 Prolabo Silica gel 60[®] (35-75 micron) suitable for flash silica gel chromatography.

Example 1**6-[[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]methyl]-2-pyridinecarboxylic acid****i) 6-Hydroxymethyl-2-pyridinecarboxylic acid, methyl ester**

A mixture of 2,6-pyridinedicarboxylic acid (10g) in thionyl chloride (40ml) with catalytic dimethylformamide was heated at reflux for 4 hours. The mixture was evaporated to dryness and azeotroped with toluene. Toluene (20ml) was added to the residue followed by methanol (20ml). The solvent was evaporated and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic phase was dried (MgSO₄) and evaporated. The residue was dissolved in methanol and sodium borohydride (0.96g) was added. The mixture was heated at reflux for 2 hours and evaporated. The residue was partitioned between chloroform and water. The organic phase was dried (MgSO₄) and evaporated. Purification was by chromatography eluting with 5% methanol in chloroform.

Yield 2.76g.

¹H NMR: δ (CDCl₃) 8.04(d,1H), 7.86(t,1H), 7.56(d,1H), 4.88(d,2H), 4.00(s,3H), 3.74(t,1H).

ii) 6-Chloromethyl-2-pyridinecarboxylic acid, methyl ester

To a solution of the product from step (i) (2.75g) in ethyl acetate (10ml) was added 1M ethereal HCl (10ml). The mixture was stirred for 10 minutes and the precipitate filtered off. This was dissolved in thionyl chloride (20ml) at 0°C. After 2 hours the mixture was warmed to room temperature. Diethyl ether (100ml) was added and the precipitate filtered off and used directly in the next step. Yield 1.3g.

iii) 5-Bromo-2,4-bis[1,1-dimethylethoxy]pyrimidine

To a solution of potassium tert-butoxide (67.5g) in tetrahydrofuran (500ml) was added dropwise a solution of 5-bromo-2,4-dichloropyrimidine (55g) (J. Am. Chem. Soc. 1934, 56, 134) in tetrahydrofuran (100ml). After 1.5 hours, water (100ml) was added carefully and the mixture extracted with ethyl acetate. The combined extract was washed with water, dried (MgSO₄) and evaporated under reduced pressure. Purification was by chromatography eluting with 5% triethylamine in isohexane. Yield 52.4g.

MS: GC-MS: 302/304 (M⁺)

iv) 5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-2,4(1*H*,3*H*)-pyrimidinedione

To a solution of 5-bromo-2,4-bis(1,1-dimethylethoxy)pyrimidine (50g) in dry tetrahydrofuran (1l) at -78°C was added *n*-butyllithium (69ml of a 2.5M solution in hexanes) dropwise. After 0.5 hours, a solution of 5*H*-dibenzo[*a,d*]cyclohepten-5-one (44g) in tetrahydrofuran (100ml) was added. The reaction mixture was stirred at -78°C for three hours and then allowed to warm to room temperature overnight. Saturated aqueous ammonium chloride solution (400ml) was added and the mixture extracted with ethyl acetate. The organic solution was dried (MgSO₄) and evaporated under reduced pressure to give the crude 5-(2,4-bis(1,1-dimethylethoxy)pyrimidin-5-yl)-5*H*-dibenzo[*a,d*]cyclohepten-5-ol which was used directly.

To a stirred solution of the 5-(2,4-bis(1,1-dimethylethoxy)pyrimidin-5-yl)-5*H*-dibenzo[*a,d*]cyclohepten-5-ol and triethylsilane (64ml) in dry dichloromethane (400ml) at 0°C was added trifluoroacetic acid (150ml) dropwise over ten minutes. The cooling bath was removed and the solution was stirred at room temperature overnight. Toluene (300 ml) was added and solution was evaporated under vacuum. The residue was azeotroped with toluene (3 times). The oil was treated with diethyl ether and the precipitated product collected as a white powder (44g).

MS: EI: 302 (M⁺, 100%)

v) 6-[[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]methyl]-2-pyridinecarboxylic acid, methyl ester

Cesium carbonate (1.63g) was added to a stirred solution of the product of step (iv) (1.5g) in dimethylsulphoxide (20ml). After 15 minutes triethylamine (0.71ml) was added followed by the product from step (ii) (1.11g). The mixture was stirred at room temperature for 4 hours and partitioned between ethyl acetate and water. The organic phase was dried (MgSO₄) and evaporated. Purification was by chromatography eluting with 5% methanol in chloroform. Yield 1.86g.

MS: APCI(+ve): 452 (M+1)

vi) 6-[[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]methyl]-2-pyridinecarboxylic acid, methyl ester

A mixture of the product from step (v) (1.84g) and Lawesson's reagent (1.65g) in 1,4-dioxane (30ml) was heated at reflux for 24 hours. The mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic phase was dried (MgSO₄) and evaporated. Purification was by chromatography eluting with 50% ethyl acetate in isohexane. Yield 1.38g.

MS: APCI(+ve): 468 (M+1)

vii) 6-[[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl)methyl]-2-pyridinecarboxylic acid

5 A mixture of the product from step (vi) (1.37g) and lithium hydroxide monohydrate (0.588g) in methanol (20ml) and water (15ml) was stirred at room temperature for 3 hours. A precipitate formed which was filtered off and partitioned between ethyl acetate and 1N HCl. The organic phase was dried (MgSO₄) and concentrated under reduced pressure to 10ml. The product was precipitated by the addition of diethyl ether. Yield 0.56g.

10 MS: APCI(+ve): 454 (M+1, 100%)

¹H NMR: δ (DMSO) 13.34(br s, 1H), 12.67(s, 1H), 8.02(d, 2H), 7.61(d, 2H), 7.49-7.23(m, 7H), 7.08(s, 1H), 6.77(s, 2H), 5.83(s, 1H), 5.00(s, 2H).

MP: 235-236°C

15 **Example 2**

2-[[6-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyridazin-3-yl]thio]acetic acid

20 **i) 5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-1-[6-chloropyridazin-3-yl]-2,4(1*H*,3*H*)-pyrimidinedione**

Cesium carbonate (2.15g) was added to a stirred solution of the product of example 1 step (iv) (2g) in dimethylsulphoxide (20ml). After 5 minutes 3,6-dichloropyridazine (1g) was added and the mixture heated at 80°C for 3 hours. The mixture was partitioned between ethyl acetate and water. The organic phase was dried (MgSO₄) and evaporated. The residue
25 was purified by chromatography eluting with 50% ethyl acetate in isohexane. Yield 1.8g.
¹H NMR: δ (DMSO) 11.70(s, 1H), 8.08(d, 1H), 8.01(d, 1H), 7.60(d, 2H), 7.42-7.28(m, 7H), 6.99(s, 2H), 5.46(s, 1H).

30 **ii) 2-[[6-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyridazin-3-yl]thio]acetic acid, methyl ester**

Methyl thioglycolate (0.97ml) was added dropwise to a stirred suspension of sodium hydride (0.434g, 60% dispersion in oil) in dimethylformamide (30ml). The mixture was stirred at room temperature for 1 hour. 13ml of this solution was added to a solution of the product from step (i) (0.9g) in dimethylformamide (20ml). The mixture was stirred for 2
35 hours then quenched with aqueous ammonium chloride and partitioned between ethyl

acetate and water. The organic phase was dried (MgSO₄) and evaporated. The residue was purified by chromatography eluting with 50% ethyl acetate in isohexane. Yield 1.0g.

¹H NMR: δ (DMSO) 11.63(s,1H), 7.81(s,2H), 7.61-7.27(m,8H), 7.14(s,1H), 6.97(s,2H), 5.45(s,1H), 4.22(s,2H), 3.67(s,3H).

5

iii) 2-[[6-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyridazin-3-yl]thio]acetic acid, methyl ester

The subtitle compound was prepared from the product of step (ii) (0.99g) by the method of example 1 step (vi). Purification was by chromatography eluting with 30-40% ethyl acetate in isohexane. Yield 0.5g.

10

MS: APCI(+ve): 501 (M+1, 100%)

iv) 2-[[6-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyridazin-3-yl]thio]acetic acid

The title compound was prepared from the product of step (iii) (0.49g) by the method of example 1 step (vii). Yield 0.345g.

15

MS: APCI(+ve): 487 (M+1, 100%)

¹H NMR: δ (DMSO) 12.96(s,1H), 7.83(s,2H), 7.68(d,2H), 7.54(s,1H), 7.43-7.27(m,6H), 7.01(s,2H), 5.98(s,1H), 4.16(s,2H).

20

MP:248-250°C

Example 3

5-[5*H*-Dibenzo[*a,d*]cyclohepten-5-yl]-1-[6-[[5-[trifluoromethyl]-1,2,4-triazol-3-yl]thio]pyridazin-3-yl]-2,4(1*H*,3*H*)-pyrimidinedione

A solution of 5-[trifluoromethyl]-4*H*-1,2,4-triazole-3(2*H*)-thione (1.6g) in dimethylformamide (10ml) was added to a stirred suspension of sodium hydride (0.336g, 60% dispersion in oil) in dimethylformamide (20ml). The mixture was stirred for 1.5 hours. 25ml of this solution were added to a solution of the product from example 2 step (i) (0.87g) in dimethylformamide (20ml). After 4 hours at room temperature the mixture was heated at 100°C for 16 hours. The mixture was partitioned between ethyl acetate and water. The organic phase was dried (MgSO₄) and evaporated. The residue was purified by chromatography eluting with 5-10% methanol in chloroform. Yield 0.4g.

30

MS: APCI(+ve): 548 (M+1, 100%)

¹H NMR: δ (DMSO) 11.67(s,1H), 7.98(d,1H), 7.88(d,1H), 7.60-7.27(m,8H), 7.22(s,1H), 6.97(s,2H), 5.45(s,1H).

35

MP:160°C

Example 4

5-[5*H*-Dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-4-thioxo-1-[6-[[5-[trifluoromethyl]-1,2,4-triazol-3-yl]thio]pyridazin-3-yl]-2(1*H*)-pyrimidinone

5 The title compound was prepared from example 3 (1.0g) by the method of example 1 step (vi). Yield 0.02g.

MS: APCI(+ve): 564 (M+1, 100%)

¹H NMR: δ (DMSO) 12.99(s,1H), 8.02(d,1H), 7.89(d,1H), 7.66-7.62(m,3H), 7.45-7.26(m,6H), 7.00(s,2H), 5.97(s,1H).

10 MP:165°C

Example 5

4-[2-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]-4-[carboxymethylthio]pyrimidin-5-yl]phenylacetic acid

15

i) 4-[Tributylstannyl]phenylacetic acid, methyl ester

A mixture of 4-bromophenylacetic acid methyl ester (1.97g) (J.Org.Chem. 1994, 59, 6095), hexabutyltin (5.0g) and tetrakis(triphenylphosphine)palladium (0) (0.46g) in toluene (60ml) was heated at reflux for 18 hours. The mixture was partitioned between ethyl acetate and aqueous ammonia. The organic phase was dried (MgSO₄) and evaporated. Purification was by chromatography eluting with 2-4% ethyl acetate in isohexane. Yield 1.21.g.

20

¹H NMR: δ (CDCl₃) 7.42(d,2H), 7.24(d,2H), 3.70(s,3H), 3.61(s,2H), 1.61-0.86(m,27H).

25 **ii) 4-[2,4-Bis-[1,1-dimethylethoxy]pyrimidin-5-yl]phenylacetic acid, methyl ester**

A mixture of the product of example 1 step (iii) (0.91g) tetrakis(triphenylphosphine)palladium (0) (0.2g) and the product from step (i) (0.75g) in toluene (25ml) was heated at reflux for 18 hours. The mixture was partitioned between diethyl ether and aqueous ammonia. The organic phase was dried (MgSO₄) and evaporated. Purification was by chromatography eluting with 10% ethyl acetate in isohexane. Yield 0.35g.

30

¹H NMR: δ (CDCl₃) 8.21(s,1H), 7.46(dt,2H), 7.30(d,2H), 3.72(s,3H), 3.66(s,2H).

iii) 4-[2,4-Dichloropyrimidin-5-yl]phenylacetic acid, methyl ester

35 Trifluoroacetic acid (1ml) was added to a solution of the product from step (ii) (1.13g) in dichloromethane (20ml) at room temperature. After 3 hours the mixture was evaporated

and the residue heated at reflux with phosphorous oxychloride (30ml) and *N,N*-dimethylaniline (0.38ml) for 14 hours. The solvent was evaporated and the residue partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic phase was dried (MgSO₄) and evaporated. Purification was by chromatography eluting with 20% ethyl acetate in isohexane. Yield 0.61g.
MS: GC-MS: 296/8/300 (M+1)

iv) 4-[2-Chloro-4-[methoxycarbonylmethylthio]pyrimidin-5-yl]phenylacetic acid, methyl ester
Methyl thioglycolate (0.18ml) was added to a solution of the product from step (iii) (0.6g) and triethylamine (0.56ml) in tetrahydrofuran (10ml) at room temperature. The mixture was stirred for 4 hours and partitioned between ethyl acetate and water. The organic phase was dried (MgSO₄) and evaporated. Purification was by chromatography eluting with 20-30% ethyl acetate in isohexane. Yield 0.7g.
MS:APCI(+ve): 367/9 (M+1)

v) 4-[2-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-4-[methoxycarbonylmethylthio]pyrimidin-5-yl]phenylacetic acid, methyl ester
The subtitle compound was prepared from the product of step (iv) (0.58g) and the product of example 1 step (iv) (0.48g) by the method of example 2 step (i). Purification was by chromatography eluting with 2% methanol in chloroform. Yield 0.4g.
MS: APCI(+ve): 633 (M+1, 100%)

vi) 4-[2-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]-4-[methoxycarbonylmethylthio]pyrimidin-5-yl]phenylacetic acid, methyl ester
The subtitle compound was prepared from the product of step (v) (0.32g) by the method of example 1 step (vi). Purification was by chromatography eluting with 30% ethyl acetate in isohexane. Yield 0.21g.
MS: APCI(+ve): 649 (M+1)

vii) 4-[2-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]-4-[carboxymethylthio]pyrimidin-5-yl]phenylacetic acid
The title compound was prepared from the product of step (vi) (0.2g) by the method of example 1 step (vii). Yield 0.11g.

MS: APCI(+ve): 621 (M+1)

¹H NMR: δ (DMSO) 12.90(s,1H), 12.70(br s,1H), 8.50(s,1H), 7.67-7.27(m,13H), 7.08(s,2H), 5.96(s,1H), 4.03(s,2H), 3.68(s,2H).

MP:280°C

5

Example 6

2-[[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]thio]acetic acid

10 **i) 1-[2-Chloropyrimidin-4-yl]-5-[5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-2,4(1*H*,3*H*)-pyrimidinedione**

A mixture of 2,4-dichloropyrimidine (1.49g), cesium carbonate (3.26g) and the product of example 1 step (iv) (3g) in dimethylsulphoxide (40ml) was stirred at room temperature for 3 hours and partitioned between ethyl acetate and water. The organic phase was dried
15 (MgSO₄) and evaporated. The product was collected after trituration with 50% ethyl acetate in isohexane. Yield 2.55g.

MS: APCI(+ve): 415/7 (M+1)

20 **ii) 2-[[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]thio]acetic acid, methyl ester**

A mixture of the product from step (i) (0.52g), methyl thioglycolate (0.18ml) and triethylamine (0.42ml) in tetrahydrofuran (10ml) was heated at reflux for 24 hours. The mixture was partitioned between ethyl acetate and 2N HCl. The organic phase was dried (MgSO₄) and evaporated. Purification was by chromatography eluting with 40% ethyl
25 acetate in isohexane. Yield 0.42g.

MS: APCI(+ve): 485 (M+1, 100%)

iii) 2-[[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]thio]acetic acid, methyl ester

30 The subtitle compound was prepared from the product of step (ii) (0.41g) by the method of example 1 step (vi). Purification was by chromatography eluting with 30% ethyl acetate in isohexane. Yield 0.21g.

¹H NMR: δ (DMSO) 12.93(s,1H), 8.67(d,1H), 8.01(s,1H), 7.80(d,1H), 7.67-7.29(m,8H), 7.04(s,2H), 5.95(s,1H), 4.03(s,2H), 3.63(s,3H).

35

iv) 2-[[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]thio]acetic acid

The title compound was prepared from the product of step (iii) (0.2g) by the method of example 1 step (vii). Purification was by chromatography eluting with 5% methanol in chloroform. Yield 0.05g.

MS: APCI(+ve): 487 (M+1, 100%)

¹H NMR: δ (DMSO) 12.94(br s,2H), 8.67(d,1H), 8.00(s,1H), 7.77(d,1H), 7.65(d,2H), 7.45-7.29(m,6H), 7.06(s,2H), 5.95(s,1H), 3.98(s,2H).

MP:190°C

Example 7

N-[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine

i) *N*-[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine, methyl ester

A mixture of the product from example 6 step (i) (1g), glycine methyl ester hydrochloride (0.339g) and *N,N*-diisopropylethylamine (1.13ml) in 1-methyl-2-pyrrolidinone (20ml) was heated at 90°C for 7 hours. The mixture was partitioned between ethyl acetate and water.

The organic phase was washed with water, dried (MgSO₄) and evaporated. The residue was dissolved in methanol/chloroform and the product precipitated by the addition of 50% ethyl acetate in isohexane. Yield 0.96g.

¹H NMR: δ (DMSO) 11.49(s,1H), 8.31(d,1H), 7.72-6.96(m,12H), 5.76(s,1H), 3.98(br s,2H), 3.71(br s,3H).

ii) *N*-[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine, methyl ester

The subtitle compound was prepared from the product of step (i) (0.955g) by the method of example 1 step (vi). Purification was by chromatography eluting with 50-60% ethyl acetate in isohexane. Yield 0.77g.

¹H NMR: δ (DMSO) 12.82(s,1H), 8.35(d,1H), 7.90-7.00(m,12H), 5.95(s,1H), 4.04(br s,2H), 3.68(br s,3H).

iii) *N*-[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine

The title compound was prepared from the product of step (ii) (0.85g) by the method of example 1 step (vii). Yield 0.63g.

5 MS: APCI(+ve): 470 (M+1, 100%)

¹H NMR: δ (DMSO) 12.82(s,1H), 8.34(d,1H), 7.88(br s,1H), 7.63(d,2H), 7.45-7.28(m,6H), 7.15(d,1H), 7.04(brs,2H), 5.96(s,1H), 3.98(d,2H). (Rotamers)

MP:208°C

10 **Example 8**

N-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine

i) 5-[2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-2,4(1*H*,3*H*)-pyrimidinedione

15 *n*-Butyllithium (5.6ml of a 2.5M solution in hexanes) was added dropwise to a solution of the product of example 1 step (iii) (3.85g) in tetrahydrofuran (30ml) at -78°C. The solution was stirred for 30 minutes and a solution of 10,11-dihydro-2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-one (European Patent, 1993, 0 589 322 A1) (3.0g) in tetrahydrofuran (20ml) was added. The mixture was stirred at -78°C for 45 minutes and
20 room temperature for 15 minutes and then partitioned between brine and ethyl acetate. The organic phase was dried (MgSO₄) and evaporated. The residue was dissolved in glacial acetic acid (100ml) and heated at 120°C for 30 minutes. The solvent was evaporated and the residue azeotroped with toluene and triturated with diethyl ether to give a solid. Yield 4.03g.

25 MS: APCI(+ve): 331 (M+1, 100%)

ii) 1-[2-Chloropyrimidin-4-yl]-5-[2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-2,4(1*H*,3*H*)-pyrimidinedione

The subtitle compound was prepared from the product of step (i) (4.0g) by the method of
30 example 6 step (i). Purification was by chromatography eluting with 50% ethyl acetate in isohexane. Yield 3.2g.

¹H NMR: δ (DMSO) 11.66(s,1H), 8.74(d,1H), 8.07(d,1H), 7.72(s,1H), 7.44(d,2H), 7.21-7.18(m,4H), 6.91(s,2H), 5.35(s,1H), 2.29(s,6H).

iii) *N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine, methyl ester

The subtitle compound was prepared from the product of step (ii) (0.5g) by the method of example 7 step (i). Yield 0.3g. Used directly in the next step.

iv) *N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine

The title compound was prepared from the product of step (iii) (0.1g) by the method of example 1 step (vii). Yield 0.09g.

MS: APCI(+ve): 482 (M+1)

¹H NMR: δ (DMSO) 11.50(s,1H), 8.32(d,1H), 7.70(br s,1H), 7.60(br s,1H), 7.40(d,2H), 7.20(d+s,4H), 7.0(br s,1H), 6.9(s,2H), 5.33(s,1H), 5.10(br s,2H), 2.30(s,6H). (Rotamers)
MP:260-263°C

Example 9

N-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine

i) *N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine, methyl ester

The subtitle compound was prepared from the product of example 8 step (iii) (0.2g) by the method of example 1 step (vi). Purification was by chromatography eluting with 30-50% ethyl acetate in isohexane. Yield 0.11g.

MS: APCI(+ve): 512 (M+1, 100%)

ii) *N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine

The title compound was prepared from the product of step (i) (0.1g) by the method of example 1 step (vii). Yield 0.02g.

MS: APCI(+ve): 498 (M+1, 100%)

¹H NMR: δ (DMSO) 12.83(s,1H), 8.35(d,1H), 7.92-6.94(m,8H), 5.89(s,1H), 4.00(s,2H), 2.29(s,6H).

MP:205°C

Example 10

2-[2-[[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid

5 **i) 2-[[2-aminoacetyl]amino]-4-thiazoleacetic acid, ethyl ester**

A mixture of *N*-(tert-butoxycarbonyl)glycine (3.1g), 2-amino-4-thiazoleacetic acid ethyl ester (3g) and bromo-tris(pyrrolidino)-phosphonium hexafluorophosphate (7.54g) in dimethylformamide (20ml) was treated with *N,N*-diisopropylethylamine (6ml). After 25 minutes *N,N*-dimethyl-4-aminopyridine (1.96g) was added. After 24 hours the mixture
10 was partitioned between ethyl acetate and brine. The organic phase was washed with saturated aqueous sodium bicarbonate, brine, 1N HCl and brine, dried (MgSO₄) and evaporated. The residue was purified by chromatography eluting with 50% ethyl acetate in isohexane. The product (0.77g) was dissolved in dichloromethane (25ml) and trifluoroacetic acid (10ml). After 2 hours the mixture was evaporated. The residue was
15 partitioned between ethyl acetate and sodium bicarbonate solution. The aqueous phase was repeatedly extracted with ethyl acetate. The combined extracts were dried (MgSO₄) and evaporated. Yield 0.41g.

MS: APCI(+ve): 244 (M+1)

20 **ii) 2-[2-[[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid, ethyl ester**

A mixture of the product from step (i) (0.194g), *N,N*-diisopropylethylamine (0.35ml) and the product from example 8 step (ii) (0.25g) in 1-methyl-2-pyrrolidinone (5ml) was heated
25 at 90°C for 10 hours. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with water, dried (MgSO₄) and evaporated. Purification was by chromatography eluting with 70% ethyl acetate in isohexane. Yield 0.175g.

MS: APCI(+ve): 650 (M+1)

30 **iii) 2-[2-[[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid**

The title compound was prepared from the product of step (ii) (0.175g) by the method of example 1 step (vii). Yield 0.03g.

MS: APCI(+ve): 622 (M+1, 100%)

35 ¹H NMR: δ (DMSO) 12.52(br s, 1H), 12.38(br s, 1H), 11.49(s, 1H), 8.31(d, 1H), 7.57-6.87(m, 11H), 5.32(s, 1H), 4.22(d, 1H), 3.64(s, 2H), 2.21(br s, 6H). (Rotamers).

MP:223°C

Example 11

***N*-[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline**

i) *N*-[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline, methyl ester

The subtitle compound was prepared from the product of example 6 step (i) (0.3g) and L-proline methyl ester hydrochloride (0.6g) by the method of example 10 step (ii).

Purification was by chromatography eluting with 5% methanol in dichloromethane. Yield 0.55g.

MS: APCI(+ve): 508 (M+1)

ii) *N*-[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline

The title compound was prepared from the product of step (i) (0.55g) by the method of example 1 step (vii) Yield 0.187g.

MS: APCI(+ve): 494 (M+1)

¹H NMR: δ (DMSO) 12.49(br s, 1H), 11.48(s, 1H), 8.30(d, 1H), 7.87(s, 1H), 7.6-7.62(m, 2H), 7.28-7.42(m, 7H), 6.99(s, 2H), 5.44(s, 1H), 4.4-4.44(m, 1H), 3.27-3.37(m, 2H), 2.3-2.37(m, 1H), 2.0-2.07(m, 3H)

MP:190-200°C

Example 12

***N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline**

i) *N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline, methyl ester

The subtitle compound was prepared from the product of example 8 step (ii) (0.3g) and L-proline methyl ester hydrochloride (0.56g) by the method of example 10 step (ii).

Purification was by chromatography eluting with 5% methanol in chloroform. Yield 0.3g.

MS: APCI(+ve): 536 (M+1, 100%)

ii) *N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline

The title compound was prepared from the product of step (i) (0.3g) by the method of example 1 step (vii). Yield 0.105g.

5 MS: APCI(+ve): 522 (M+1, 100%)

¹H NMR: δ (DMSO) 8.30(d,1H), 7.87(s,1H), 7.45(d,2H), 7.32(d,1H), 7.22-7.18(m,3H), 6.89(s,2H), 5.33(s,1H), 4.42(m,1H), 3.36 (m,3H), 2.35(m,1H), 2.29(s,6H), 2.04-2.07(m,3H).

MP:200-205°C

10

Example 13

(2*S-trans*)-*N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-4-hydroxy-2-pyrrolidinecarboxylic acid

- 15 i) (2*S-trans*)-*N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-4-hydroxy-2-pyrrolidinecarboxylic acid, phenylmethyl ester

The subtitle compound was prepared from *trans*-4-hydroxy-L-proline benzyl ester hydrochloride (0.928g) and the product of example 8 step (ii) (0.3g) by the method of example 10 step (ii). Purification was by chromatography eluting with 50-60% ethyl acetate in isohexane. Yield 0.29g.

20

MS: APCI(+ve): 429 (M+1)

- 25 ii) (2*S-trans*)-*N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-4-hydroxy-2-pyrrolidinecarboxylic acid

The title compound was prepared from the product of step (i) (0.28g) by the method of example 1 step (vii). Yield 0.05g.

MS: APCI(+ve): 538 (M+1)

¹H NMR: δ (DMSO) 11.46(s,1H), 8.30(d,1H), 7.87(s,1H), 7.45(d,2H), 7.32(d,1H), 7.22-7.15(m,4H), 6.91(s,2H), 5.34(s,1H), 4.50(brs,1H), 4.43(t,1H), 3.49(dd,1H), 3.41-3.37(m,1H), 2.30(s,6H), 2.31-2.00(m,1H), 2.16-2.07(m,1H).

30

MP:208-210°C

Example 14

N^α-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-histidine

- 5 i) *N*^α-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-histidine, methyl ester

The subtitle compound was prepared from L-histidine methyl ester dihydrochloride (1.15g) and the product of example 8 step (ii) (0.7g) by the method of example 10 step (ii).

Purification was by chromatography eluting with 5-10% methanol in dichloromethane.

- 10 Yield 0.25g.

MS: APCI(+ve): 576 (M+1)

- ii) *N*^α-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-histidine

- 15 The title compound was prepared from the product of step (i) (0.122g) by the method of example 1 step (vii). Yield 0.025g.

MS: APCI(+ve): 562 (M+1)

¹H NMR: δ (DMSO, 90°C) 11.19(s, 1H), 8.26(d, 1H), 7.80(s, 1H), 7.65(s, 1H), 7.39(m, 2H), 7.19-7.12(m, 6H), 6.97-6.83(m, 3H), 5.31(s, 1H), 4.60(m, 1H), 3.12(s, 2H), 2.28(s, 6H).

- 20 MP: 223°C

Example 15

(±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid

25

- i) 3-Ethylphenylmethanol

- n-Butyllithium (34ml of a 2.5M solution in hexanes) was added to a solution of 1-bromo-3-ethylbenzene (15g) in tetrahydrofuran (320ml) at -78°C. After 1 hour dimethylformamide (15ml) was added. The mixture was stirred at -78°C for 1 hour and allowed to warm to room temperature. The mixture was quenched with aqueous ammonium chloride and partitioned between ethyl acetate and water. The organic phase was dried (MgSO₄) and evaporated. The residue was dissolved in methanol (250ml) and treated with sodium borohydride (1.51g) portionwise. The mixture was stirred at room temperature for 16 hours, quenched with 2M HCl (100ml) and stirred for 4 hours. The mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate and
- 35

2M HCl. The organic phase was dried (MgSO_4), evaporated and the residue purified by chromatography eluting with 5-10% ethyl acetate in isohexane. Yield 7.6g.

MS: GC-MS: 136 (M^+) 97%

5 **ii) 1-Bromomethyl-3-ethylbenzene**

Phosphorous tribromide (5.3ml) was added to a solution of the product from step (i) (7.6g) in benzene (150ml) at 0°C. After 3 hours, water (40ml) was added and the mixture warmed to room temperature and extracted with ethyl acetate. The organic phase was dried (MgSO_4) and evaporated. Purified by chromatography eluting with 2% ethyl acetate in isohexane. Yield 8.0g.

^1H NMR: δ (CDCl_3) 7.28-7.12(m,4H), 4.48(s,2H), 2.65(q,2H), 1.24(t,3H).

iii) 2-[2,4-Dimethylphenyl]-4,5-dihydro-4,4-dimethyloxazole

Dimethylformamide (8 drops) was added to a stirred suspension of 2,4-dimethylbenzoic acid (80g) in thionyl chloride (400ml) and the mixture was stirred overnight at room temperature. The solution was heated at 80°C for 3 hours and the thionyl chloride evaporated. The residue was dissolved in dichloromethane (200ml) and added dropwise to a solution of 2-amino-2-methyl-propan-1-ol (124ml) in dichloromethane (400ml). The mixture was stirred overnight, washed with 2M HCl, water, aqueous sodium bicarbonate and water. The organic phase was dried (MgSO_4) and evaporated. The residue was dissolved in dichloromethane (800ml) and treated with thionyl chloride (125ml) dropwise at 0°C. The mixture was stirred at room temperature for 2 hours and evaporated. The solid residue was partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic phase was washed with water, dried (MgSO_4) and evaporated. Yield 69g.

^1H NMR: δ (CDCl_3) 7.64(d,1H), 7.02-6.99(m,2H), 4.04(s,2H), 2.52(s,3H), 2.32(s,3H), 1.38(s,6H).

iv) 2-[2-[2-[3-Ethylphenyl]ethyl]-4-methylphenyl]-4,5-dihydro-4,4-dimethyloxazole

n-Butyllithium (16.8ml of a 2.5M solution in isohexane) was added dropwise to a stirred solution of the product of step (iii) (8.13g) in dry tetrahydrofuran (150ml) at 0°C under nitrogen. After 1 hour, the product of step (ii) (8.0g) in tetrahydrofuran (60ml) was added. After 1 hour, the reaction was quenched with aqueous ammonium chloride and partitioned between ethyl acetate and water. The organic solution was dried (MgSO_4) and evaporated. Purification was by chromatography eluting with 5% ethyl acetate in isohexane. Yield 4.93g.

MS: APCI+: 322 ($\text{M}+1$)

v) 2-[2-[3-Ethylphenyl]ethyl]-4-methylbenzoic acid

The product of step (iv) (4.9g) and methyl iodide (4.7ml) in acetonitrile (150ml) was heated under reflux for 6 hours. The solution was evaporated and the residue and sodium hydroxide (8g) was refluxed in water (40ml) and methanol (50ml). After 6 hours the methanol was evaporated and the residue was partitioned between ethyl acetate and 2M hydrochloric acid. The organic solution was dried (MgSO₄) and evaporated. Used directly in the next step.

vi) 2-Ethyl-10,11-dihydro-8-methyl-5H-dibenzo[a,d]cyclohepten-5-one

A mixture of the product from step (v) in polyphosphoric acid (40g) and sulfolane (20ml) was heated at 130°C for 5 hours and partitioned between ethyl acetate and water. The organic phase was washed with aqueous sodium bicarbonate and water, dried (MgSO₄) and evaporated. Purified by chromatography eluting with 5% ethyl acetate in isohexane.

MS: GC-MS: 250 (M⁺)

vii) (±)-5-[2-Ethyl-8-methyl-5H-dibenzo[a,d]cyclohepten-5-yl]-2,4(1H,3H)-pyrimidinedione

The subtitle compound was prepared from the product of step (vi) (3g) by the method of example 8 step (i). Yield 1.48g.

MS: LC-MS: APCI(+ve): 345 (M+1, 100%)

viii) (±)-1-[2-Chloropyrimidin-4-yl]-5-[2-ethyl-8-methyl-5H-dibenzo[a,d]cyclohepten-5-yl]-2,4(1H,3H)-pyrimidinedione

The subtitle compound was prepared from the product of step (vii) (0.44g) by the method of example 6 step (i). Yield 0.42g.

¹H NMR: δ (DMSO) 11.66(s,1H), 8.74(d,1H), 8.08(d,1H), 7.73(s,1H), 7.48-7.43(m,2H), 7.24-7.19(m,4H), 6.92(s,2H), 5.36(s,1H), 2.60(q,2H), 2.29(s,3H), 1.17(t,3H).

ix) (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5H-dibenzo[a,d]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid, ethyl ester

The subtitle compound was prepared from the products of step (viii) (0.415g) and example 10 step (i) (1g) by the method of example 10 step (ii). Purification was by chromatography eluting with 70-80% ethyl acetate in isohexane. Yield 0.22g.

MS: APCI(+ve): 664 (M+1, 100%)

x) **(±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl amino]-4-thiazoleacetic acid**

The title compound was prepared from the product of step (ix) (0.21g) by the method of example 1 step (vii). Yield 0.12g.

MS: APCI(+ve): 636 (M+1, 100%)

¹H NMR: δ (DMSO) 12.50(br s, 1H), 12.37(s, 1H), 11.48(s, 1H), 8.31(d, 1H), 7.59(s, 1H), 7.45-6.88(m, 11H), 5.33(s, 1H), 4.22(d, 2H), 3.64(s, 2H), 2.53(br s, 2H), 2.22(br s, 3H), 1.17(br s, 3H).

MP: 217°C

Example 16

2-[2-[[2-[Dimethylamino]-4-[5-{2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-6-yl]amino]acetyl amino]-4-thiazoleacetic acid

i) **1-[2,6-Dichloropyrimidin-4-yl]-5-[2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-2,4(1*H*,3*H*)-pyrimidinedione**

Cesium carbonate (5g) was added to a solution of the product of example 8 step (i) (5g) in 1-methyl-2-pyrrolidinone (50ml). After 5 minutes 2,4,6-trichloropyrimidine (2.8g) was added. After 2 hours the reaction was partitioned between brine and ethyl acetate. The organic phase was washed with water, dried (MgSO₄) and evaporated under reduced pressure. Purification was by chromatography eluting with 30% ethyl acetate in toluene. Yield 2.9g.

MS: APCI(+ve): 477 (M+1)

ii) **2-[2-[[2-Chloro-4-[5-{2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-6-yl]amino]acetyl amino]-4-thiazoleacetic acid, ethyl ester**

A mixture of the product of step (i) (1.5g), the product of example 10 step (i) (1.13g) and *N,N*-diisopropylethylamine (0.6ml) in 1-methyl-2-pyrrolidinone (30ml) was heated at 50°C for 14 hours then 80°C for 4 hours. The reaction mixture was partitioned between brine containing dilute HCl and ethyl acetate. The organic phase was washed with water, dried (MgSO₄) and evaporated under reduced pressure. Purification was by chromatography eluting with 50% ethyl acetate in isohexane. Yield 0.43g.

MS: APCI(+ve): 684 (M+1)

iii) 2-[2-[[2-[Dimethylamino]-4-[5-{2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-6-yl]amino]acetylamino]-4-thiazoleacetic acid, ethyl ester

5 A mixture of the product of step (ii) (0.4g), dimethylamine hydrochloride (0.18g) and *N,N*-diisopropylethylamine (0.5ml) in dimethylformamide (5ml) was heated at 85°C for 6 hours. The reaction mixture was partitioned between brine containing dilute HCl and ethyl acetate. The organic phase was washed with water, dried (MgSO₄) and evaporated under reduced pressure. Purification was by chromatography eluting with ethyl acetate. Yield
10 0.2g.

MS: APCI(+ve): 693 (M+1)

iv) 2-[2-[[2-[Dimethylamino]-4-[5-{2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-6-yl]amino]acetylamino]-4-thiazoleacetic acid

15 The title compound was prepared from the product of step (iii) (0.2g) by the method of example 1 step (vii). Yield 0.15g.

MS: APCI(+ve): 665 (M+1)

1H NMR: δ (DMSO, at 90°C) 11.93(br s, 2H), 11.02(br s, 1H), 7.42(s, 1H), 7.40(d, 2H),
20 7.18(m, 4H), 6.93(s, 1H), 6.70(s, 2H), 6.68(t, 1H), 6.33(s, 1H), 5.28(s, 1H), 4.15(d, 2H), 3.62(s, 2H), 2.94(s, 6H), 2.25(s, 6H).

MP: 220°C

Example 17

25 *N*-[2-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-5-[methoxycarbonyl]pyrimidin-4-yl]glycine

i) 2,4-Dichloro-5-pyrimidinecarboxylic acid, methyl ester

1,2,3,4-Tetrahydro-2,4-dioxo-5-pyrimidinecarboxylic acid methyl ester (7.0g) in
30 phosphorus oxychloride (80ml) was heated under reflux for 16 hours. The phosphorus oxychloride was removed by evaporation under reduced pressure. The reaction mixture was partitioned between water and ethyl acetate. The organic phase was washed with water, dried (MgSO₄) and evaporated under reduced pressure. Purification was by chromatography eluting with 20% ethyl acetate in isohexane. Yield 4.5g.

35 1H NMR: δ (DMSO) 9.05(s, 1H), 4.0(s, 3H)

ii) 2-Chloro-4-[[[1,1-dimethylethoxy]carbonylmethyl]amino]-5-pyrimidinecarboxylic acid, methyl ester

A mixture of the product of step (i) (1.73g), glycine tert-butyl ester (1.4g) and *N,N*-diisopropylethylamine (2.6ml) in dimethylformamide (20ml) was stirred at room temperature. After 4 hours, the reaction mixture was partitioned between 2M HCl and ethyl acetate. The organic phase was washed with water, dried (MgSO₄) and evaporated under reduced pressure. Purification was by chromatography eluting with 5% ethyl acetate in toluene. Yield 1.5g.

MS: APCI(+ve): 302/304 (M+1)

iii) 2-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-4-[[[1,1-dimethylethoxy]carbonylmethyl]amino]-5-pyrimidinecarboxylic acid, methyl ester

A mixture of the product of step (ii) (0.52g), the product of example 8 step (i) (0.5g) and cesium carbonate (0.49g) in dimethylformamide (15ml) was heated at 70°C. After 3 hours, the reaction mixture was partitioned between 1M HCl and ethyl acetate. The organic phase was washed with water, dried (MgSO₄) and evaporated under reduced pressure.

Purification was by chromatography eluting with 3% methanol in chloroform. Yield 0.47g.

MS: APCI(+ve): 596 (M+1)

iv) *N*-[2-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-5-[methoxycarbonyl]pyrimidin-4-yl]glycine

A mixture of the product of step (iii) (0.57g) in trifluoroacetic acid (5ml) and dichloromethane (10ml) was stirred at room temperature for 5 hours. Methanol (30ml) was added and the precipitate collected. The solid was dissolved in methanol and sodium hydroxide solution and the product precipitated out by addition of 2M HCl. Yield 0.26g.

MS: APCI(+ve): 540 (M+1, 100%)

¹H NMR: δ (DMSO) 13.02(br s, 1H), 11.39(s, 1H), 8.74(s, 1H), 8.71(t, 1H), 7.42(d, 2H), 7.19-7.17(m, 5H), 6.91(s, 2H), 5.31(s, 1H), 4.15(d, 2H), 3.86(s, 3H), 2.28(s, 6H).

Example 18

4-[[Carboxymethyl]amino]-2-[5-{2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-5-pyrimidinecarboxylic acid

The title compound was prepared from the product of example 17 step (iv) (0.23g) by the method of example 1 step (vii). Yield 0.085g.

MS: APCI(+ve): 526 (M+1, 100%)

¹H NMR: δ (DMSO) 13.34(br s, 1H), 13.00(br s, 1H), 11.38(s, 1H), 8.83(t, 1H), 8.71(s, 1H), 7.42(d, 2H), 7.19-7.15(m, 5H), 6.91(s, 2H), 5.31(s, 1H), 4.16(d, 2H), 2.28(s, 6H).

MP: 271°C

5

Example 19

(\pm)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*N*-methylglycine

i) *N*-[4-Fluoropyrimidin-2-yl]-*N*-methylglycine, methyl ester

- 10 To a solution of 2,4-difluoropyrimidine (J.Heterocyclic Chem. 1985, 22, 149) (4.48g) in isohexane (50ml) at 0°C was added sarcosine methyl ester hydrochloride (5.39g) followed by *N,N*-diisopropylethylamine (13.45ml). After 5 minutes, the ice bath was removed and the reaction mixture allowed to stir at room temperature for 3 hours. The solvents were evaporated under reduced pressure and the residue purified by chromatography eluting
15 with ethyl acetate/isohexane mixtures. The first and minor component of the mixture to be eluted was the subtitle compound. Yield 0.68g.

MS: APCI(+ve): 200 (M+1)

- ii) (\pm)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*N*-methylglycine, methyl ester
20

- A mixture of the product of step (i) (0.68g), and the product of example 15 step (vii) (2.35g) was stirred with cesium carbonate (2.22g) in 1-methyl-2-pyrrolidinone (20ml) at 70-80°C for 4 hours. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was dried (MgSO₄) and evaporated under reduced pressure. The residue
25 was purified by chromatography eluting with ethyl acetate in toluene. Yield 0.57g.

MS: APCI(+ve) 524 (M+1)

iii) (\pm)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*N*-methylglycine, methyl ester

- 30 The subtitle compound was prepared from the product of step (ii) (0.57g) according to the method of example 1 step (vi). Purification was by chromatography eluting with 10% ethyl acetate in toluene. Yield 0.33g.

MS: APCI(+ve) 540 (M+1)

iv) **(±)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*N*-methylglycine**

The title compound was prepared from the product of step (iii) (0.33g) by the method of example 1 step (vii). Yield 0.23g.

5 MS: APCI(+ve) 526 (M+1)

¹H NMR: δ (DMSO at 90°C) 12.40(s, 2H), 8.39(d, 1H), 8.05(s, 1H), 7.5(m, 2H), 7.20(m, 5H), 6.90(dd, 2H), 5.94(s, 1H), 4.33(s, 2H), 3.10(s, 3H), 2.60(q, 2H), 2.30(s, 3H), 1.20(t, 3H).

MP: 187°C

10

Example 20

(±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methylamino]acetylaminol-4-thiazoleacetic acid

15

i) 2-[2-[Methylamino]acetylaminol-4-thiazoleacetic acid, ethyl ester

The subtitle compound was prepared from *N*-tert-butoxycarbonyl sarcosine (6.0g) and 2-amino-4-thiazoleacetic acid ethyl ester (6.6g) by the method of example 10 step (i). Yield 5.24g

20

¹H NMR: δ(D₂O) 6.96(s, 1H), 4.10-4.03(m, 4H), 3.69(s, 2H), 2.72(s, 3H), 1.11(t, 3H).

ii) 2-[2-[[4-Fluoropyrimidin-2-yl][methylamino]acetylaminol-4-thiazoleacetic acid, ethyl ester

The product of step (i) (3.0g) was slurried in dichloromethane (100ml) and treated with *N,N*-diisopropylethylamine (4.0ml) forming a complete solution. 2,4-Difluoropyrimidine (J. Heterocyclic Chem. 1985, 22, 149) (0.6g) was then added quickly with stirring. After 10 minutes the solvents were evaporated under reduced pressure and the residue purified by chromatography eluting with 20% ethyl acetate in isohexane. The first and minor component of the mixture to be eluted was the subtitle compound (0.77g).

30

MS: APCI(-ve): 352 (M-1).

iii) (±)-5-[2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-4-thioxo-2(1*H*)-pyrimidinone

The subtitle compound was prepared from the product of example 15 step (vii) (0.83g) by the method of example 1 step (vi). Yield 0.58g.

35

MS: APCI(+ve): 361 (M+1)

iv) (±)-5-[2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-4-methylthio-2(1*H*)-pyrimidinone

The product of step (iii) (0.58g) was dissolved in ethanol (30ml) and water (5ml) and treated with sodium bicarbonate(0.14g) and iodomethane (0.2ml) and stirred for 24 hours. The reaction mixture was partitioned between ethyl acetate and brine. The organic phase was dried (MgSO₄) and solvent evaporated under reduced pressure. The residue was triturated with isohexane and filtered to give the product. Yield 0.41g.
MS: APCI(+ve): 375(M+1), APCI(-ve): 359(M-15)

v) (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-4-methylthio-2-oxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid, ethyl ester

The product of step (iv) (0.37g), and the product of step (ii) (0.35g) was stirred with cesium carbonate (0.32g) in dry 1-methyl-2-pyrrolidinone (15ml) at 65-70° C for 20 hours. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer collected, dried (MgSO₄), and solvent evaporated under reduced pressure. Yield 0.61g.
MS: APCI(+ve): 708(M+1)

vi) (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid, ethyl ester

The product from step (v) (0.61g) was dissolved in dry pyridine (20ml) and triethylamine (1.0ml). Hydrogen sulphide gas was slowly bubbled through the solution for 15 minutes. The solvents were evaporated under reduced pressure and the residue azeotropeed twice with toluene. The residue was purified by chromatography eluting with ethyl acetate in toluene. Yield 0.41g.
MS: APCI(+ve): 694(M+1)

vii) (±)-2-[2-[*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*N*-methylamino]acetyl]amino]-4-thiazoleacetic acid

The title compound was obtained from the product of step (vi) (0.41g) according to the method of example 1 step (vii). Yield 0.2g.
MS: APCI(+ve): 666 (M+1)

¹H NMR: δ(DMSO at 90° C) 12.80(br s, 1H), 12.32(br s, 2H), 8.36(d, 1H), 8.08(s, 1H), 7.49(m, 2H), 7.25(d, 1H), 7.20(m, 4H), 6.90(m, 3H), 5.92(s, 1H), 4.55(s, 2H), 3.62(s, 2H), 3.20(s, 3H), 2.60(q, 2H), 2.30(s, 3H), 1.11(t, 3H)

MP: 205° C

5

Example 21

2-[2-[[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid

- 10 **i) 2-[2-[[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid, ethyl ester**

The subtitle compound was prepared from the product of example 8 step (ii) (0.6g) and the product of example 20 step (i) (1.31g) by the method of example 7 step (i). Purification
15 was by precipitation with ether and filtration. Yield 0.60g

MS: APCI(+ve): 664 (M+1, 100%)

- 20 **ii) 2-[2-[[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid**

The title compound was prepared from the product of step (i) (0.19g) by the method of example 1 step (vii). Yield 0.097g.

MS: APCI(+ve): 636 (M+1)

25 ¹H NMR: δ(DMSO, 90° C) 12.07 (br s, 2H), 11.10 (s, 1H), 8.31 (d, 1H), 7.78 (br s, 1H), 7.41 (d, 2H), 7.25 (d, 1H), 7.17-7.13 (m, 4H), 6.93 (s, 1H), 6.86 (s, 2H), 5.33 (s, 1H), 4.52 (s, 2H), 3.60 (s, 2H), 3.05 (s, 3H), 2.26 (s, 6H).

MP: 210° C

Example 22

(±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid

5

i) (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid, ethyl ester

The subtitle compound was prepared from the product of example 15 step (viii) (0.5g) and the product of example 20 step (i) (0.73g) by the method of example 7 step (i).

Purification was by precipitation with ethyl acetate/isohehexane and filtration. Yield 0.59g.

MS: APCI(+ve): 678 (M+1)

ii) (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid

15

The title compound was prepared from the product of step (i) (0.58g) by the method of example 1 step (vii). Yield 0.424g.

MS: APCI(+ve): 650 (M+1)

1H NMR: δ(DMSO, 90° C) 12.07(br s, 2H), 11.20(br s, 1H), 8.30(d, 1H), 7.80(s, 1H), 7.45-7.40(m, 2H), 7.26-7.14(m, 5H), 6.93(s, 1H), 6.93-6.84(m, 2H), 5.34(s, 1H), 4.52(s, 2H), 3.60(s, 2H), 3.05(s, 3H), 2.58(q, 2H), 2.26(s, 3H), 1.16(t, 3H).

MP: 188°C

25 **Example 23**

(±)-2-[2-[[4-[3,4-Dihydro-5-{2-methoxy-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid

30 i) 4,5-Dihydro-2-[2-[2-[3-Methoxyphenyl]ethyl]-4-methylphenyl]-4,4-dimethyloxazole

The subtitle compound was prepared from the product of example 15 step (iii) (20g) and 3-methoxybenzyl chloride (17.4ml) by the method of example 15 step (iv). Purification was by chromatography eluting with 5-10% ethyl acetate in isohehexane. Yield 20.53g.

35 MS: APCI(+ve): 324 (M+1).

ii) 2-[2-[3-Methoxyphenyl]ethyl]-4-methylbenzoic acid

The subtitle compound was prepared from the product of step (i) (20.53g) by the method of example 15 step (v). Used directly in the next step.

MS: APCI(-ve): 269 (M-1).

5

iii) 10,11-Dihydro-2-methoxy-8-methyl-5H-dibenzo[a,d]cyclohepten-5-one

The subtitle compound was prepared from the product of step (ii) by the method of example 15 step (vi). Purified by chromatography eluting with 5-10% ethyl acetate in isohexane. Yield 10.56g.

10 MS: APCI(+ve): 253 (M+1).

iv) (±)-5-[2-Methoxy-8-methyl-5H-dibenzo[a,d]cyclohepten-5-yl]-2,4(1H,3H)-pyrimidinedione

15 The subtitle compound was prepared from the product of step (iii) (10.5g) by the method of example 8 step (i). Purified by chromatography eluting with 60-70% ethyl acetate in isohexane. Yield 3.25g.

MS: APCI(+ve): 347 (M+1).

v) (±)-1-[2-Chloropyrimidin-4-yl]-5-[2-methoxy-8-methyl-5H-dibenzo[a,d]cyclohepten-5-yl]-2,4(1H,3H)-pyrimidinedione

20 The subtitle compound was prepared from the product of step (iv) (1.0g) by the method of example 6 step (i). Purified by chromatography eluting with 40-50% ethyl acetate in isohexane. Yield 0.57g.

MS: APCI(+ve): 459 (M+1).

25

vi) (±)-2-[2-[[4-[3,4-Dihydro-5-{2-methoxy-8-methyl-5H-dibenzo[a,d]cyclohepten-5-yl}-2,4-dioxo-1(2H)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid, ethyl ester

30 The subtitle compound was prepared from the product of step (v) (0.56g) by the method of example 7 step (i). Purified by precipitation from ethyl acetate/ isohexane. Yield 0.54g

MS: APCI(+ve): 680 (M+1).

vii) (±)-2-[2-[[4-[3,4-Dihydro-5-{2-methoxy-8-methyl-5H-dibenzo[a,d]cyclohepten-5-yl}-2,4-dioxo-1(2H)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid

35

The title compound was prepared from the product of step (vi) (0.53g) by the method of example 1 step (vii). Yield 0.38g.

MS: APCI(+ve): 652 (M+1).

¹H NMR: δ (DMSO, 90°C) 12.06(br s, 2H), 11.20(s, 1H), 8.31(d, 1H), 7.79(s, 1H),
5 7.45(d, 1H), 7.41(d, 1H), 7.25(d, 1H), 7.17(d, 1H), 7.14(s, 1H), 6.96-6.90(m, 3H), 6.87(s, 2H),
5.32(s, 1H), 4.52(s, 2H), 3.74(s, 3H), 3.60(s, 2H), 3.06(s, 3H), 2.27(s, 3H).
MP: 186°C

Example 24

10 (±)*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-3-azetidinecarboxylic acid

The title compound was prepared from the product of example 15 step (viii) (0.2g) and 3-azetidinecarboxylic acid (0.045g) by the method of example 7 step (i). Purification was by precipitation with ethyl acetate/isohexane and filtration. Yield 0.14g.

15 MS: APCI(+ve): 522 (M+1)

¹H NMR: δ (DMSO) 12.79(s, 1H), 11.46(s, 1H), 8.34(d, 1H), 7.79(d, 1H), 7.48-7.18(m, 7H),
6.95-6.86(m, 2H), 5.33(s, 1H), 4.17(br m, 2H), 4.00(br m, 2H), 3.63-3.53(m, 1H), 2.59(q, 2H),
2.28(s, 3H), 1.16(t, 3H).

MP: 244°C

20

Example 25

2-[2-[[6-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-4-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid

25

i) 5-[2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-4-thioxo-2(1*H*)-pyrimidinone

The subtitle compound was prepared from the product of example 8 step (i) (0.60g) by the method of example 1 step (vi). Purification was by chromatography eluting with 30-50%
30 ethyl acetate in isohexane. Yield 0.22g.

MS: APCI(+ve): 347 (M+1)

ii) 5-[2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-4-methylthio-2(1*H*)-pyrimidinone

35 Iodomethane (0.2ml) was added to a stirred suspension of the product from step (i) (0.65g) and sodium bicarbonate (0.4g) in ethanol (15ml) and water (4ml). After stirring for 30min,

the reaction mixture was washed with water, 1M hydrochloric acid, aqueous sodium bicarbonate, water, dried (MgSO₄) and evaporated under reduced pressure. The residue was triturated with ether and filtered. Yield 0.49g.

MS: APCI(+ve): 361 (M+1)

5

iii) 1-[6-Chloropyrimidin-4-yl]-5-[2,8-dimethyl-5H-dibenzo[*a,d*]cyclohepten-5-yl]-4-methylthio-2(1*H*)-pyrimidinone

The subtitle compound was prepared from the product of step (ii) (0.33g) and 4,6-dichloropyrimidine (0.149g) by the method of example 16 step (i). Purification was by chromatography eluting with 30% ethyl acetate in isohexane. Yield 0.23g.

¹H NMR: δ(DMSO) 8.98(d,1H), 8.24(d,1H), 7.61(d,1H), 7.53(d,2H), 7.24(d,2H), 7.23(s,2H), 6.95(s,2H), 5.41(s,1H), 2.42(s,3H), 2.30(s,6H).

iv) 2-[2-[[6-[5-{2,8-Dimethyl-5H-dibenzo[*a,d*]cyclohepten-5-yl}-4-methylthio-2-oxo-1(2*H*)-pyrimidinyl]pyrimidin-4-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid, ethyl ester

A mixture of the product from step (iii) (0.22g), the product from example 20 step (i) (0.252g) and *N,N*-diisopropylamine (0.4ml) in 1-methyl-2-pyrrolidinone (4ml) was stirred at room temperature overnight. The reaction mixture was partitioned between 1M hydrochloric acid and ethyl acetate. The organic layer was washed with water, dried (MgSO₄) and evaporated under reduced pressure. Used directly in the next step.

MS: APCI(+ve): 694 (M+1)

v) 2-[2-[[6-[5-{2,8-Dimethyl-5H-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-4-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid, ethyl ester

The subtitle compound was prepared from the product of step (iv) by the method of example 20 step (vi). Yield 0.21g.

MS: APCI(+ve): 680 (M+1)

30

vi) 2-[2-[[6-[5-{2,8-Dimethyl-5H-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-4-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid

The title compound was prepared from the product of step (v) (0.20g) by the method of example 1 step (vii). Yield 0.106g.

MS: APCI(+ve): 652 (M+1).

35

¹H NMR: δ (DMSO) 12.92(s,1H), 12.35(s,2H), 8.42(s,1H), 7.88(s,1H), 7.48(d,2H), 7.18-7.15(2xs,5H), 6.95(s,1H), 6.91(s,2H), 5.89(s,1H), 4.55(br s,2H), 3.60(s,2H), 3.09(s,3H), 2.27(s,6H).

MP:215°C

5

Example 26

(\pm)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*L*-proline

- 10 i) (\pm)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*L*-proline, methyl ester

The subtitle compound was prepared from the product of example 15 step (viii) (0.5g) and *L*-proline methyl ester hydrochloride (0.265g) by the method of example 10 step (ii).

Purification was by chromatography eluting with 40% ethyl acetate in isohexane. Yield

15 0.47g.

MS: APCI(+ve): 550 (M+1).

- ii) (\pm)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*L*-proline

- 20 The title compound was prepared from the product of step (i) (0.16g) by the method of example 1 step (vii). Yield 0.03g.

MS: APCI(+ve): 536 (M+1).

¹H NMR: δ (DMSO, 90°C) 12.17(s,1H), 11.18(s,1H), 8.29(d,1H), 7.85(br s,1H), 7.46-7.40(m,2H), 7.24-7.16(m,5H), 6.96-6.83(m,2H), 5.32(s,1H), 4.43(d,1H), 3.42(br s,2H),
25 2.60(q,2H), 2.38-2.29(m,1H), 2.29(s,3H), 2.05-2.02(br m,3H), 1.18(t,3H).

MP:185°C

Example 27

- 30 (\pm)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*L*-proline

- i) (\pm)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*L*-proline, methyl ester

- 35 The subtitle compound was prepared from the product of example 26 step (i) (0.3g) by the method of example 1 step (vi). Purification was by chromatography eluting with 20-40% ethyl acetate in isohexane. Yield 0.25g.

MS: APCI(+ve): 566 (M+1).

ii) (\pm) -*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*L*-proline

5 The title compound was prepared from the product of step (i) (0.25g) by the method of example 1 step (vii). Yield 0.085g.

MS: APCI(+ve): 552 (M+1).

¹H NMR: δ (DMSO, 90°C) 12.51(s,1H), 12.20(s,1H), 8.33(d,1H), 8.10(br s,1H), 7.53-7.47(m,2H), 7.30-7.16(m,5H), 7.00-6.89(m,2H), 5.85(s,1H), 4.47(d,1H), 3.48(br s,2H),
10 2.59(q,2H), 2.38-2.32(m,1H), 2.28(s,3H), 2.05 (br s,3H), 1.17(t,3H).

MP:175°C

Example 28

15 (\pm) -2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-9*H*-purine-9-acetic acid.

i) *N*-[2-Chloro-5-nitropyrimidin-4-yl]glycine, 1,1-dimethylethyl ester.

A stirred mixture of 2,4-dichloro-5-nitropyrimidine (1.00g) (J.Chem.Soc. 1951, 1568),
N,N-diisopropylethylamine (0.89g), isohexane (10ml) and dichloromethane (10ml) was
20 treated portionwise over 10 minutes at 0°C with glycine t-butyl ester hydrochloride (0.58g).

The mixture was stirred at 0°C for 2 hours and evaporated. Purification was by chromatography eluting with 10% ethyl acetate in isohexane. Yield 0.9g.

MS: APCI(-ve): 288 (M-1)

25 ii) (\pm) -*N*-[2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-5-nitropyrimidin-4-yl]glycine, 1,1-dimethylethyl ester

To a stirred suspension of sodium hydride (60% dispersion in oil, 116mg) in 1-methyl-2-pyrrolidinone (10ml) was added the product of example 15 step (vii) (1.00g). After 0.5 hours the solution was treated with the product from step (i) (0.838g) and stirred overnight.
30 The mixture was diluted with brine and extracted with ethyl acetate. The combined extracts were dried (MgSO₄) and evaporated. Purification was by chromatography eluting with 15% ethyl acetate in toluene. Yield 0.89g.

MS: APCI(-ve): 596 (M-1)

35 iii) (\pm) -*N*-[5-Amino-2-[5-{2-ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-4-yl]glycine, 1,1-dimethylethyl ester.

A mixture of the product from step (ii) (0.766g), iron powder (1g), ammonium chloride (1g), water (5ml) and methanol (20ml) was stirred and heated under reflux for 2 hours and filtered through celite. The pad was washed with methanol and the combined filtrates were evaporated. The residue was taken up in ethyl acetate, was washed with water, dried
5 (MgSO₄) and evaporated to give an oil. The oil was crystallised from warm ethyl acetate. Yield 0.558g.

MS: APCI(+ve): 567 (M+1)

iv) (±)-2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-9*H*-purine-9-acetic acid, 1,1-dimethylethyl ester.
10

A mixture of the product from step (iii) (478mg) and diethoxymethyl acetate (0.5ml) was stirred at 90°C for 15 hours, diluted with methanol and evaporated. Purification was by chromatography eluting with ethyl acetate. Yield 0.28g.

1H NMR: δ (DMSO) 11.52(s,1H), 9.28(s,1H), 8.75(s,1H), 7.5-7.6(m,6H), 7.2-7.3(m,4H),
15 7.2(s,1H), 6.94 (d,2H), 5.4(s,1H), 5.14(s,2H), 2.62(q,2H), 2.32(s,3H), 1.47(s,9H), 1.21(t,3H).

v) (±)-2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-9*H*-purine-9-acetic acid.

20 A solution of the product from step (iv) (0.26g) in trifluoroacetic acid (5ml) and dichloromethane (10ml) was stirred overnight and evaporated. The residue was triturated with ether and filtered off. Yield 0.21g.

MS: APCI(+ve): 521 (M+1)

1H NMR: δ 11.45(s,1H), 9.21(s,1H), 8.69(s,1H), 7.41-7.47(m,2H), 7.16-7.26(m,4H),
25 7.06(s,1H), 6.90(br s,1H), 5.34(s,1H), 5.12(s,2H), 2.57(q,2H), 2.26(s,3H), 1.14(t,3H).
MP: 212-220°C

Example 29

N-[2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-5-nitropyrimidin-4-yl]glycine.
30

A solution of the product from example 28 step (ii) (0.07g) in dichloromethane (1ml) and trifluoroacetic acid (1ml) was stirred overnight and evaporated. The residue was triturated with ether and filtered off. Yield 0.05g.

MS: APCI(+ve): 541 (M+1)

¹H NMR: δ (DMSO) 13.12(br s, 1H), 11.48(s, 1H), 9.19(t, 1H), 9.15(s, 1H), 7.41-7.47(m, 2H), 7.18-7.24(m, 4H), 6.93(br s, 2H), 5.33(s, 1H), 4.21(d, 2H), 2.59(q, 2H), 2.28(s, 3H), 1.16(t, 3H).

MP: >240°C

5

Example 30

(\pm)-2-[2-[[4-[3,4-dihydro-5-{2-methyl-8-[1-methylethyl]-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid

10

i) 4,5-Dihydro-4,4-dimethyl-2-[4-[1-methylethyl]phenyl]oxazole

The subtitle compound was prepared from 4-[1-methylethyl]benzoic acid (25.3g) using the method of example 15 step (iii). Yield 26.13g.

MS: APCI(+ve): 218(M+1, 100%)

15

ii) 4,5-Dihydro-4,4-dimethyl-2-[2-methyl-4-[1-methylethyl]phenyl]oxazole

n-Butyllithium (52.8ml of a 2.5M solution in hexane) was added dropwise to a stirred solution of the product of step (i) (27.6g) in tetrahydrofuran (100ml) at -20°C. After 2 hours methyl iodide (85.3g) was added and the mixture was stirred for 2 hours at this temperature then 0.5 hours at room temperature. The reaction mixture was partitioned between brine and ethyl acetate. The aqueous solution was extracted with ethyl acetate. The organic solution was dried (MgSO₄) and evaporated under reduced pressure. Purification was by chromatography eluting with 5% ethyl acetate in isohexane. Used directly in the next step.

20

iii) 4,5-Dihydro-4,4-dimethyl-2-[4-[1-methylethyl]-2-[2-[3-methylphenyl]ethyl]phenyl]oxazole

The subtitle compound was prepared from the product of step (ii) and 3-bromomethyltoluene (9.25g) using the method of example 15 step (iv). Purification was by chromatography eluting with toluene. Yield 4.8g.

25

MS: APCI(+ve): 336(M+1, 100%)

iv) 4-[1-Methylethyl]-2-[2-[3-methylphenyl]ethyl]benzoic acid

The subtitle compound was made from the product of step (iii) (4.85g) using the method of example 15 step (v). Yield 3.43g.

30

MS: APCI(-ve): 281 (M-1, 100%)

v) **10,11-Dihydro-2-methyl-8-[1-methylethyl]-5H-dibenzo[*a,d*]cyclohepten-5-one**

The subtitle compound was prepared from the product of step (iv) (3.36g) using the method of example 15 step (vi). Yield 2.73g.

5 MS: APCI(+ve): 265 (M+1, 100%)

vi) **(±)-5-[2-Methyl-8-[1-methylethyl]-5H-dibenzo[*a,d*]cyclohepten-5-yl]-2,4(1*H*,3*H*)-pyrimidinedione**

10 The subtitle compound was prepared from the product of step (v) (2.73g) using the method of example 8 step (i). Yield 2.8g. Used directly in the next step.

vii) **(±)-1-[2-Chloropyrimidin-4-yl]-5-[2-methyl-8-[1-methylethyl]-5H-dibenzo[*a,d*]cyclohepten-5-yl]-2,4(1*H*,3*H*)-pyrimidinedione**

15 The subtitle compound was prepared from the product of step (vi) (1.00g) by the method of example 6 step (i). Purification was by chromatography eluting with 20% ethyl acetate in toluene. Yield 0.373g

MS: APCI(+ve): 471 (M+1)

20 viii) **(±)-2-[2-[[4-[3,4-Dihydro-5-{2-methyl-8-[1-methylethyl]-5H-dibenzo[*a,d*]cyclohepten-5-yl]-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl amino]-4-thiazoleacetic acid, ethyl ester.**

The subtitle compound was prepared from the product of step (vii) (373mg) using the method of example 10 step (ii). Purification was by chromatography eluting with 60% ethyl acetate in toluene. Yield 0.13g.

25 MS: APCI(+ve): 678 (M+1)

ix) **(±)-2-[2-[[4-[3,4-Dihydro-5-{2-methyl-8-(1-methylethyl)-5H-dibenzo[*a,d*]cyclohepten-5-yl]-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl amino]-4-thiazoleacetic acid**

30 The title compound was prepared from the product of step (viii) (0.12g) by the method of example 1 step (vii). Purification was by recrystallisation from a mixture of ethyl acetate and isohexane. Yield 0.04g.

MS: APCI(+ve): 649 (M+1)

1H NMR: δ (DMSO, 90°C) 12.06(br s, 2H), 11.21(br s, 1H), 8.29(d, 1H), 7.65(s, 1H), 7.35-
35 7.44(m, 2H), 7.12-7.24(m, 6H), 6.89-6.98(m, 3H), 5.33(s, 1H), 4.23(d, 2H), 3.61(s, 3H), 2.80-2.91(m, 1H), 2.24(s, 3H), 1.16(d, 6H).

MP: 215-220°C

Example 31

(±)-2-[2-[[4-[3,4-Dihydro-5-{2-methyl-8-propyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid

i) 1-Bromo-3-propylbenzene

A solution of 3'-bromopropiophenone (25g) and triethylsilane (57ml) in trifluoroacetic acid (50ml) was heated at reflux for 16 hours. The reaction mixture was evaporated under reduced pressure and the residue was purified by chromatography eluting with isohexane. Yield 25.14g. The subtitle compound was contaminated with 17 mole% of 3-(1-propenyl)bromobenzene. Used directly in the next step.

¹H NMR: δ(CDCl₃) 7.32(m,2H), 7.10(m,2H), 2.55(t,2H), 1.61(m,2H), 0.90(t,3H).

ii) 3-Propylphenylmethanol

The subtitle compound was prepared from the product of step (i) (24.14g) by the method of example 15 step (i). Used directly in the next step. Yield 15.8g.

iii) 1-Bromomethyl-3-propylbenzene

The subtitle compound was prepared from the product of step (ii) (15.8g) by the method of example 15 step (ii). Purification was by chromatography eluting with isohexane. Yield 11.7g. The subtitle compound was contaminated with 15 mole% of 1-bromomethyl-3-(1-propenyl)benzene. Used directly in the next step.

¹H NMR: δ(CDCl₃) 7.30-7.10(m,4H), 4.49(d,2H), 2.60(m,2H), 1.65(m,2H), 0.95(m,3H).

iv) 4,5-Dihydro-4,4-dimethyl-2-[4-methyl-2-[2-[3-propylphenyl]ethyl]phenyl]oxazole.

The subtitle compound was prepared from the product of step (iii) (11.7g) and the product of example 15 step (iii) (11.2g) by the method of example 15 step (iv). Purification was by chromatography eluting with 12% ethyl acetate in isohexane. Yield 15.4g. The subtitle compound was contaminated with 14 mole% of 4,5-dihydro-4,4-dimethyl-2-[4-methyl-2-[2-[3-(1-propenyl)phenyl]ethyl]phenyl]oxazole. Used directly in the next step.

MS: APCI(+ve): 336 (M+1, 100%).

v) 4-Methyl-2-[2-[3-propylphenyl]ethyl]benzoic acid

The subtitle compound was prepared from the product of step (iv) (15.4g) by the method of example 15 step (v). The crude reaction product was contaminated with 4-methyl-2-[2-[3-

[1-propenyl]phenyl]ethyl]benzoic acid. The crude reaction product was dissolved in ethyl acetate (100ml) and the solution was hydrogenated over 10% palladium on carbon (1g) at 3 atmospheres pressure for 2 hours. The catalyst was removed by filtration and the filtrate was evaporated. Yield 12.8g.

5 MS: APCI(-ve): 281 (M-1, 100%).

vi) 10,11-Dihydro-2-methyl-8-propyl-5H-dibenzo[a,d]cyclohepten-5-one.

The subtitle compound was prepared from the product of step (v) (12.8g) by the method of example 15 step (vi). Purification was by chromatography eluting with isohexane. Yield
10 7.36g.

MS: APCI(+ve): 265 (M+1, 100%).

vii) (±)-5-[2-Methyl-8-propyl-5H-dibenzo[a,d]cyclohepten-5-yl]-2,4(1H,3H)-pyrimidinedione.

15 The subtitle compound was prepared from the product of step (vi) (7.0g) by the method of example 8 step (i). Yield 7.30g.

MS: APCI(+ve): 359 (M+1).

viii) (±)-1-[2-Chloropyrimidin-4-yl]-5-[2-methyl-8-propyl-5H-dibenzo[a,d]cyclohepten-5-yl]-2,4(1H,3H)-pyrimidinedione.

The subtitle compound was prepared from the product of step (vii) (2.50g) by the method of example 6 step (i). Purification was by chromatography eluting with 40% ethyl acetate in isohexane. Yield 0.80g.

MS: APCI(+ve): 471 (M+1, 100%).

25

ix) (±)-2-[2-[[4-[3,4-Dihydro-5-{2-methyl-8-propyl-5H-dibenzo[a,d]cyclohepten-5-yl}-2,4-dioxo-1(2H)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid, ethyl ester

The subtitle compound was prepared from the products of step (viii) (0.40g) and example
30 10 step (i) (0.80g) by the method of example 10 step (ii). Purification was by chromatography eluting with 66% ethyl acetate in isohexane. Yield 0.29g.

MS: APCI(+ve): 678 (M+1, 100%).

x) (±)-2-[2-[[4-[3,4-Dihydro-5-{2-methyl-8-propyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl amino]-4-thiazoleacetic acid.

The title compound was prepared from the product of step (ix) (0.29g) by the method of example 1 step (vii). Yield 0.123g.

MS: APCI(+ve): 650 (M+1, 100%)

¹H NMR: δ (DMSO, 90°C) 11.17(s,1H), 8.29(d,1H), 7.65(s,1H), 7.37(t,2H), 7.3-7.1(m,6H), 6.96(s,1H), 6.92(q,2H), 5.32(s,1H), 4.23(s,2H), 3.61(s,2H), 2.24(s,3H), 1.55(sextet,2H), 0.85(t,3H).

MP: 198-200 °C.

Example 32

(±)-*N*-[4-[3,4-Dihydro-5-{2-methyl-8-propyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*N*-methylglycine

i) (±)-*N*-[4-[3,4-Dihydro-5-{2-methyl-8-propyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*N*-methylglycine, methyl ester

The subtitle compound was prepared from the product of example 31 step (viii) (0.39g) and sarcosine methyl ester hydrochloride (0.23g) by the method of example 7 step (i).

Purification was by chromatography eluting with 40% ethyl acetate in isohexane. Yield 0.18g.

MS: APCI(+ve): 538 (M+1, 100%)

ii) (±)-*N*-[4-[3,4-Dihydro-5-{2-methyl-8-propyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*N*-methylglycine, methyl ester

The subtitle compound was prepared from the product of step (i) (0.18g) by the method of example 1 step (vi). Purification was by chromatography eluting with 12.5% ethyl acetate in toluene. Yield 0.08g.

MS: APCI(+ve): 554 (M+1, 100%)

iii) (±)-*N*-[4-[3,4-Dihydro-5-{2-methyl-8-propyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*N*-methylglycine

The title compound was prepared from the product of step (ii) by the method of example 1 step (vii). The product was precipitated by the addition of isohexane/ethyl acetate. Yield 0.04g.

MS: APCI(+ve): 540 (M+1, 100%)

¹H NMR: δ (DMSO, 90°C) 12.49 (br s, 1H), 8.36 (d, 1H), 8.02 (s, 1H), 7.49 (t, 2H), 7.24 (d, 1H), 7.17 (s, 4H), 6.91 (s, 2H), 5.90 (s, 1H), 4.31 (s, 2H), 3.07 (s, 3H), 2.5 (m, 2H), 2.28 (s, 3H), 1.58 (sextet, 2H), 0.88 (t, 3H).

MP: 145-150 °C

5

Example 33

(\pm)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl amino]-5-thiazoleacetic acid

10

i) 4-Oxobutanoic acid, ethyl ester

Ethyl succinyl chloride (4.1g) was added to a suspension of 10% palladium on carbon (0.3g) and 2,6-lutidine (2.9ml) in dry tetrahydrofuran (100ml). The mixture was hydrogenated at 3 atmospheres pressure for 24 hours. The reaction mixture was filtered and the filtrate

15 evaporated under reduced pressure. Yield 3.15g.

¹H NMR: δ (CDCl₃) 9.82 (s, 1H), 4.16 (q, 2H), 2.80 (t, 2H), 2.63 (t, 2H), 1.26 (t, 3H).

ii) 3-Bromo-4-oxobutanoic acid ethyl ester.

A mixture of bromine (1.24ml) and dry 1,4-dioxane (25ml) gave an orange suspension; the solid was dissolved by the addition of diethyl ether (25ml). This solution was then added dropwise under nitrogen to a solution of the product of step (i) (3.15g) in dry 1,4-dioxane (25ml) at such a rate as to effect decolourisation of the reaction mixture before addition of the next drop. After the addition was complete the reaction mixture was stirred for 0.5 hours then diluted with water and diethyl ether. The aqueous phase was separated and

20 extracted with diethyl ether. The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure. Yield 3.53g.

¹H NMR: δ (CDCl₃) 9.54 (s, 1H), 4.68 (t, 1H), 4.20 (q, 2H), 3.22 (dd, 1H), 2.90 (dd, 1H), 1.28 (t, 3H).

30 iii) 2-Amino-5-thiazoleacetic acid ethyl ester.

A mixture of thiourea (1.28g) and the product of step (ii) (3.53g) was heated at 80°C for 1 hour. The reaction mixture was diluted with water and washed with diethyl ether. The aqueous phase was basified to pH9 by the addition of concentrated aqueous ammonia and the resultant suspension was extracted with ethyl acetate. The ethyl acetate extracts were

35 dried (MgSO₄) and evaporated under reduced pressure. Yield 2.15g.

MS: APCI(+ve): 187 (M+1, 100%)

iv) 2-[2-Aminoacetyl-amino]-5-thiazoleacetic acid ethyl ester

The subtitle compound was prepared from the product of step (iii) (1.86g) and *N*-(tert-butoxycarbonyl)glycine (1.75g) by the method of example 10 step (i). Yield 3.13g.

5 MS: APCI(+ve): 244 (M+1, 100%).

v) (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl-amino]-5-thiazoleacetic acid, ethyl ester

10 The subtitle compound was prepared from the product of step (iv) (1.05g) and the product from example 15 step (viii) (0.5g) by the method of example 10 step (ii). Purification was by chromatography eluting with 66-100% ethyl acetate in toluene. Yield 0.27g.

MS: APCI(+ve): 664 (M+1, 100%).

vi) (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl-amino]-5-thiazoleacetic acid

The title compound was prepared from the product of step (v) (0.27g) by the method of example 1 step (vii). Yield 0.13g.

20 MS: APCI(+ve): 636 (M+1, 100%)

¹H NMR: δ (DMSO, 90°C) 8.29 (d,1H), 7.66 (s,1H), 7.41 (d,1H), 7.38 (d,1H), 7.25 (br s,2H), 7.20-7.10 (m,5H), 6.92 (d,2H), 5.33 (s,1H), 4.23 (d,2H), 3.71 (s,2H), 2.56 (q,2H), 2.24 (s,3H), 1.14 (t,3H).

MP: 206-208°C

25

Example 34

(±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl-amino]-4-thiazolecarboxylic acid.

30

i) 2-[2-[Methylamino]acetyl-amino]-4-thiazolecarboxylic acid ethyl ester.

The subtitle compound was prepared from *N*-(tert-butoxycarbonyl)sarcosine (1.99g) and 2-amino-4-thiazole carboxylic acid ethyl ester (J.Heterocyclic Chem. 1989.26,1643) (2.0g) by the method of example 10 step (i) Yield 2.47g.

35 MS: APCI(-ve): 242 (M-1)

ii) (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazolecarboxylic acid ethyl ester.

The subtitle compound was prepared from the product of step (i) (1.05g) and the product from example 15 step (viii) (0.5g) by the method of example 10 step (ii). Purification was by chromatography eluting with 33% toluene in ethyl acetate. Yield 0.37g.

MS: APCI(-ve): 663 (M-1)

iii) (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazolecarboxylic acid.

The title compound was prepared from the product of step (ii) (0.15g) by the method of example 1 step (vii). Yield 0.070g.

MS: APCI(-ve): 635 (M-1)

¹H NMR: δ (DMSO) 12.87(s,1H), 12.62(s,1H), 11.48(s,1H), 8.31(d,1H), 7.98(s,1H), 7.86(s,1H), 7.46(s,2H), 7.30(m,1H), 7.22-7.18(m,4H), 6.92(s,2H), 5.36(s,1H), 4.55(s,2H), 3.05(s,3H), 2.60(m,1H), 2.28(s,3H), 1.16(m,3H).

MP: 213-6°C (dec.)

Example 35

(±)-2-[[1-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]azetidin-3-yl]carbonylamino]-4-thiazoleacetic acid

i) (±)-2-[[1-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]azetidin-3-yl]carbonylamino]-4-thiazoleacetic acid, ethyl ester

The subtitle compound was prepared from the product of example 15 step (viii) (0.53g) according to the method of example 10 step (ii). Yield 0.52g

MS: APCI(+ve): 690 (M+1)

ii) (±)-2-[[1-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]azetidin-3-yl]carbonylamino]-4-thiazoleacetic acid

The title compound was prepared from the product of step (i) (0.52g) according to the method of example 1 step (vii). Yield: 0.3g

MS: APCI(+ve): 662 (M+1), APCI(-ve): 660 (M-1)

¹H NMR: δ (DMSO): 12.45(br s, 1H), 12.37(br s, 1H), 11.46(br s, 1H), 8.36(d, 1H), 7.76(s, 1H), 7.45(m, 2H), 7.30(d, 1H), 7.20(m, 4H), 7.0(s, 1H), 6.90(dd, 2H), 5.32(s, 1H), 4.25(m, 2H), 4.10(m, 2H), 3.88(m, 1H), 3.62(s, 2H), 2.50(q, 2H), 2.30(s, 3H), 1.10(t, 3H).

5 MP: 235°C

Example 36

(\pm)-2-[2-[[4-[3,4-Dihydro-5-{2-hydroxy-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl amino]-4-thiazoleacetic acid.

10

i) (\pm)-5-[2-Hydroxy-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-2,4(1*H*,3*H*)-pyrimidinedione

A solution of borontribromide (1.0M in dichloromethane) (10ml) was added to a mixture of the product from example 23 step (iv) (1.4g) in dichloromethane (20ml). After stirring for 2 hours, the reaction mixture was partitioned between 2M hydrochloric acid and ethyl acetate. The organic layer was washed with water, dried (MgSO₄) and evaporated under reduced pressure. Used directly in the next step.

15

MS: APCI(+ve): 333 (M+1).

20

ii) (\pm)-5-[2-[[1,1-dimethylethyl]dimethylsiloxy]-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-2,4(1*H*,3*H*)-pyrimidinedione

Tert-butyl dimethylsilylchloride (0.98g) was added to a mixture of the product from step (i) and imidazole (0.74g) in dimethylformamide (20ml). The reaction mixture was stirred for 3 hours and partitioned between water and ethyl acetate. The organic layer was washed with water, dried (MgSO₄) and evaporated under reduced pressure. Purification was by chromatography eluting with 50-70% ethyl acetate in isohexane. Yield 0.71g.

25

MS: APCI(+ve): 447 (M+1).

30 iii) (\pm)-1-[2-Chloropyrimidin-4-yl]-5-[2-[[1,1-dimethylethyl]dimethylsiloxy]-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-2,4(1*H*,3*H*)-pyrimidinedione

The subtitle compound was prepared from the product of step (ii) (0.70g) by the method of example 6 step (i). Purified by chromatography eluting with 30-40% ethyl acetate in isohexane. Yield 0.76g.

35 MS: APCI(+ve): 559 (M+1).

iv) (±)-2-[2-[[4-[3,4-Dihydro-5-{2-hydroxy-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl amino]-4-thiazoleacetic acid, ethyl ester

The subtitle compound was prepared from the product of step (iii) (0.75g) by the method of example 7 step (i). Purified by chromatography eluting with 70-100% ethyl acetate in isohexane. Yield 0.34g.

MS: APCI(+ve): 652 (M+1).

v) (±)-2-[2-[[4-[3,4-Dihydro-5-{2-hydroxy-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl amino]-4-thiazoleacetic acid.

The title compound was prepared from the product of step (iv) (0.33g) by the method of example 1 step (vii). Yield 0.14g.

MS: APCI(+ve): 624 (M+1)

¹H NMR: δ (DMSO, 90°C) 12.03(br s, 1H), 11.20(s, 1H), 8.29(d, 1H), 7.60(s, 1H), 7.36-7.28(m, 3H), 7.13-7.10(m, 3H), 6.95(s, 1H), 6.90-6.74(m, 4H), 5.24(s, 1H), 4.29-4.18(m, 2H), 3.61(s, 2H), 2.23(s, 3H).

MP: 203°C (dec.)

Example 37

(±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl amino]-α-[methoxyimino]-4-thiazoleacetic acid

i) 2-[2-[Methylamino]acetyl amino]-α-[methoxyimino]-4-thiazoleacetic acid, ethyl ester

The subtitle compound was prepared from *N*-[tert-butoxycarbonyl]sarcosine (2.00g) and ethyl 2-amino-α-[methoxyimino]-4-thiazoleacetate (2.66g) by the method of example 10 step (i). Yield 2.77g.

MS: APCI(+ve): 301(M+1, 100%)

ii) 2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]- α -[methoxyimino]-4-thiazoleacetic acid, ethyl ester

The subtitle compound was prepared from the product of step (i) (0.7g) and the product of example 15 step (viii) (0.5g) by the method of example 7 step (i). The product was purified by chromatography eluting with 30% ethyl acetate in toluene. Yield 0.28g.

MS:APCI(+ve): 721(M+1,80%)

iii) 2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]- α -[methoxyimino]-4-thiazoleacetic acid

The title compound was prepared from the product of step (ii) (0.28g) by the method of example 1 step (vii). Product was a 3:1 mixture of Z:E isomers. Yield 0.2g.

MS: APCI(-ve): 691 (M-1)

¹H NMR: δ (DMSO,90°C)

signals corresponding to Z-isomer: 12.50(br s,1H)

signals corresponding to E-isomer: 12.40(br s,1H), 4.00(s,3H)

combined signals: 11.21(s,1H), 8.30(d,1H), 7.90-7.70(br s,1H), 7.50-7.40(m,3H), 7.25(d,1H),7.20-7.10(m,4H), 6.90(d,1H),6.86(d,1H), 5.34(s,1H), 4.55(s,2H), 3.91(s,3H), 3.05(s,3H), 2.57(q,2H), 2.62(s,3H), 1.13(t,3H).

Example 38

(\pm)-*N*-[(1*H*)-Tetrazol-5-yl]-1-[4-[5-{2-ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-3-azetidinecarboxamide

The title compound was prepared from example 24 (0.42g) and 5-aminotetrazole monohydrate (0.11g) by the method of example 10 step (i). Yield 0.16g.

MS: APCI(+ve): 589 (M+1)

¹H NMR: δ (DMSO) 16.00(br s,1H), 12.39(br s,1H), 11.47(br s,1H), 8.37(d,1H),

7.80(s,1H), 7.46(t,2H), 7.33(d,1H), 7.20(m,4H), 6.94(dd,2H), 5.33(s,1H), 4.20(m,2H), 4.10(br s,1H), 3.90(m,2H), 2.50(m,2H), 2.22(s,3H), 1.10(m,3H).

MP: 252°C

Example 39

(±)-2-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino-*N*-[4-[1*H*-tetrazol-5-ylmethyl]thiazol-2-yl]acetamide

5

i) 2-Amino-4-thiazoleacetamide

A solution of 2-amino-4-thiazoleacetic acid ethyl ester (15g) in methanol (75ml) and 0.880 ammonia (75ml) was stirred at room temperature for 72 hours then evaporated to dryness and triturated with toluene. Yield 11g.

10 MS: APCI(+ve): 158 (M+1,100%)

ii) 2-Amino-4-thiazoleacetonitrile

A mixture of the product from step (i) (9.5g) and phosphorous oxychloride (30ml) was heated at 90°C for 2 hours. The mixture was evaporated under reduced pressure and poured
15 onto a mixture of ice water and ethyl acetate. The aqueous phase was adjusted to pH 9 with sodium bicarbonate and extracted repeatedly with ethyl acetate. The combined extract was dried (MgSO₄) and evaporated. The residue was purified by chromatography eluting with ethyl acetate. Yield 6.1g.

¹H NMR: δ (DMSO) 7.08(br s,2H), 6.40(s,1H), 3.77(s,2H).

20

iii) 2-Amino-*N*-[4-cyanomethylthiazol-2-yl]acetamide

The subtitle compound was prepared from the product of step (ii) (3g) by the method of example 10 step (i). Yield 1.58g.

MS: APCI(+ve) 197 (M+1)

25

iv) (±)-*N*-[4-Cyanomethylthiazol-2-yl]-2-[[4-[5-{2-ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetamide

The subtitle compound was prepared from the product of step (iii) (1.58g) and the product
30 of example 15 step (viii) (1.14g) by the method of example 7 step (i). Yield 0.7g.

MS: APCI(+ve): 617 (M+1,100%)

35

v) (±)-2-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino-*N*-[4-[1*H*-tetrazol-5-ylmethyl]thiazol-2-yl]acetamide

A mixture of the product of step (iv) (0.35g) and trimethyltin azide (0.5g) in toluene (10ml) was heated at reflux for 48 hours. Methanol was added and the resultant precipitate filtered off. The solution was evaporated to dryness and the residue purified by reverse phase chromatography. The fraction containing product was concentrated under reduced pressure, acidified with 2N HCl and extracted with ethyl acetate. The extract was evaporated to dryness and the residue triturated with diethyl ether. The product was collected by filtration. Yield 0.16g.

MS: APCI(+ve): 660 (M+1, 100%)

¹H NMR: δ (DMSO, 90°C) 12.01(br s, 1H), 11.17(s, 1H), 8.28(d, 1H), 7.63(d, 1H), 7.50-7.35(m, 2H), 7.30-7.10(m, 6H), 7.00(s, 1H), 6.91(s, 2H), 5.32(s, 1H), 4.32(d, 2H), 4.21(d, 2H), 2.55(q, 2H), 2.24(s, 3H), 1.13(t, 3H).

Example 40

(\pm)[[5-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetylamino]-3-(1,2,4-thiadiazole)]acetic acid

i) [5-Amino-3-(1,2,4-thiadiazole)]acetic acid, methyl ester

A solution of [5-(ethoxycarbonylamino)-3-(1,2,4-thiadiazole)]acetic acid (Bull. Chem. Soc. Jpn. 1994, 67, 1701) (6.70g) and sodium hydroxide (2.43g) in water (100ml) was heated at reflux overnight and lyophilised. The residue was treated with a solution of acetyl chloride (21.3ml) in methanol (200ml). The solution was stirred overnight and evaporated. The residue was dissolved in water (100ml), basified with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The extract was dried (MgSO₄) and evaporated and the residue purified by chromatography eluting with ethyl acetate. Yield 0.5g.

MS: APCI(+ve) 174 (M+1, 100%)

ii) [5-[[[(1,1-Dimethylethoxy)carbonyl]amino]methyl]carbonylamino]-3-(1,2,4-thiadiazole)]acetic acid, methyl ester

The subtitle compound was prepared from the product of step (i) by the method of example 10 step (i).

MS: APCI(+ve) 231 (M+1, 100%)

iii) (±)[[5-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl amino]-3-(1,2,4-thiadiazole)]acetic acid, methyl ester

The subtitle compound was prepared from the product of step (ii) and example 15 step (viii) by the method of example 7 step (i).

MS: APCI (+ve) 651 (M+1, 100%)

iv) (±)[[5-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl amino]-3-(1,2,4-thiadiazole)]acetic acid

The title compound was prepared from the product of step (iii) by the method of example 1 step (vii).

MS: 637 (M+1, 100%)

¹H NMR: δ (DMSO, 90°C) 11.49 (br s, 1H), 8.30 (d, 1H), 7.64 (d, 1H), 7.43-7.36 (m, 2H), 7.30-7.20 (m, 1H), 7.18-7.13 (m, 5H), 6.91 (br s, 2H), 5.32 (s, 1H), 4.31 (d, 2H), 3.79 (s, 2H), 2.55 (q, 2H), 2.35 (s, 3H), 1.14 (t, 3H).

MP: 210-212°C

Example 41

(±)2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-4-pyrimidinecarboxylic acid

i) 2,6-Dichloro-4-pyrimidinecarboxylic acid, (1,1-dimethylethyl) ester

A mixture of orotic acid (43g) and phosphorous oxychloride (350ml) was heated at reflux for 72 hours and evaporated. The residue was dissolved in tetrahydrofuran (300ml) and treated with *tert*-butanol (150ml). The solution was stirred at room temperature for 1 hour and potassium *tert*-butoxide (23g) was added. The mixture was stirred at room temperature overnight and evaporated. The residue was partitioned between diethyl ether and water. The organic phase was washed with aqueous sodium bicarbonate and water, dried (MgSO₄) and evaporated. Yield 9.4g.

MS: APCI (-ve) 248/250 (M-1) 191 (100%)

ii) 2-Chloro-6-propylthio-4-pyrimidinecarboxylic acid, (1,1-dimethylethyl) ester

To a stirred solution of the product from step (i) (5.2g) and triethylamine (4.2ml) in dichloromethane (30ml) at 0°C was added propanethiol (0.9ml). The mixture was stirred for 2 hours at 0°C, warmed to room temperature and stirred for a further 2 hours. The

reaction mixture was partitioned between diethyl ether and 1M NaOH solution. The organic phase was dried (MgSO₄) and evaporated and the residue purified by chromatography eluting with 30-60% toluene in isohexane. Yield 3.84g. ¹H NMR δ (CDCl₃) 7.61 (s,1H), 3.21 (t,2H), 1.83-1.71 (m,2H), 1.60 (s,9H), 1.06 (t,3H).

5 **iii) 2-Chloro-4-pyrimidinecarboxylic acid, (1,1-dimethylethyl) ester**

To a suspension of Raney® nickel (50% slurry in water, 10g) in ethanol (20ml) was added a solution of the product from step (ii) (3.83g) in ethanol (20ml). The mixture was stirred for 2 hours and treated with a further 5g Raney® nickel. The mixture was stirred overnight and treated with a further 20g Raney® nickel. After 1 hour the reaction mixture was filtered through Kieselguhr and the filtrate evaporated. The residue was purified by chromatography eluting with 5-10% ethyl acetate in isohexane. Yield 1.3g. ¹H NMR δ (CDCl₃) 8.82 (d,1H), 7.85 (d,1H), 1.63 (s,9H).

15 **iv)(±) 2-[5-{2-Ethyl-8-methyl-5H-dibenzo[a,d]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-4-pyrimidinecarboxylic acid, (1,1-dimethylethyl) ester**

The subtitle compound was prepared from the product of step (iii) and the product of example 15 step (vii) by the method of example 19 step (ii).

MS: APCI (+ve) 523 (M+1) 467 (100%)

20 **v) (±)2-[5-{2-Ethyl-8-methyl-5H-dibenzo[a,d]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-4-pyrimidinecarboxylic acid**

The title compound was prepared from the product of step (iv) by the method of example 17 step (iv).

25 MS: APCI (-ve) 465 (M-1,100%)

¹H NMR: δ (DMSO) 9.10 (d,1H), 7.98 (d,1H), 7.47-7.42 (2xd, 2H), 7.22-7.13 (m,5H), 6.95-6.87 (q,2H), 5.34 (s,1H), 2.57 (q,2H), 2.27 (s,3H), 1.16 (t,3H).

Example 42

30 **(±)N-[[[2-[5-{2-Ethyl-8-methyl-5H-dibenzo[a,d]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]pyrimidin-4-yl]carbonyl]glycine**

i) (±)N-[[[2-[5-{2-Ethyl-8-methyl-5H-dibenzo[a,d]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]pyrimidin-4-yl]carbonyl]glycine, methyl ester

35 The subtitle compound was prepared from example 41 and glycine methyl ester by the method of the first stage of example 10 step (i).

MS: APCI (+ve) 538 (M+1,100%)

ii) (±)*N*-[[[2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-4-yl]carbonyl]glycine

5 The title compound was prepared from the product of step (i) by the method of example 1 step (vii).

MS: APCI (+ve) 524 (M+1,100%)

1H NMR: δ (DMSO) 12.84 (s,1H), 11.54 (s,1H), 9.12 (d,1H), 8.90 (t,1H), 8.01 (d,1H),
7.46 (d,1H), 7.42 (d,1H), 7.22-7.16 (m,4H), 7.11 (s,1H), 6.99-6.90 (q,2H), 5.34 (s,1H),
10 4.02 (d,2H), 2.57 (q,2H), 1.15 (t,3H).

MP: 195-8°C

Example 43

(±)2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-
15 1(2*H*)-pyrimidinyl]-*N*-[(1*H*)-tetrazol-5-yl]-4-pyrimidinecarboxamide

The title compound was prepared from example 41 and 5-aminotetrazole by the method of the first stage of example 10 step (i).

MS: APCI (+ve) 534 (M+1) 506 (100%)

1H NMR: δ (DMSO) 12.25 br s,1H), 11.58 (s,1H), 9.21 (d,1H), 8.12 (d,1H), 7.47 (d,1H),
20 7.43 (d,1H), 7.22-7.17 (m,5H), 6.98-6.91 (q,2H), 5.36 (s,1H), 2.55 (q,2H), 2.25 (s,3H),
1.12 (t,3H).

Example 44

(±)2-[[6-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-
25 dioxo-1(2*H*)-pyrimidinyl]pyridazin-3-yl]thio]acetic acid

i) (±)5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-1-[6-chloropyridazin-3-yl]-2,4(1*H*,3*H*)-pyrimidinedione

30 The subtitle compound was prepared from the product of example 15 step (vii) by the method of example 2 step (i).

1H NMR (CDCl₃) δ 8.25 (s,1H), 7.71 (d,1H), 7.43 (m,4H), 7.16 (m,4H), 6.90 (dd,2H),
5.37 (s,1H), 4.17 (s,2H), 3.79 (s,3H), 2.62 (q,2H), 2.31 (s,3H), 1.21 (t,3H).

ii) **(±)2-[[6-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyridazin-3-yl]thio]acetic acid**

The title compound was prepared from the product of step (i) by the method of example 1 step (vii).

5 MS: APCI (+ve) 513 (M+1, 100%)

¹H NMR δ (DMSO) 12.89 (br s, 1H), 11.59 (s, 1H), 7.78 (s, 2H), 7.45 (m, 2H), 7.19 (m, 5H), 6.90 (s, 2H), 5.35 (s, 1H), 4.13 (s, 2H), 2.58 (q, 2H), 2.28 (s, 3H), 1.17 (t, 3H).

MP: 225-230°C

10 **Example 45**

(±)2-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]-*N*-[(1*H*)-tetrazol-5-yl]acetamide

15 **i) 2-[(1,1-Dimethylethoxy)carbonyl]amino-*N*-[(1*H*)-tetrazol-5-yl]acetamide, pyrrolidinium salt**

To a solution of *N*-(*tert*-butoxycarbonyl)glycine (2g), 5-aminotetrazole monohydrate (1.4g) and bromo-tris(pyrrolidino)-phosphonium hexafluorophosphate (7.52g) in dimethylformamide (20ml) was added *N,N*-diisopropylethylamine (4.4g) followed by *N,N*-dimethyl-4-aminopyridine (1.4g). After 16 hours the reaction mixture was diluted with
20 ethyl acetate and washed with water and brine. The aqueous phase was adjusted to pH4 with tartaric acid and extracted repeatedly with ethyl acetate. The combined extract was dried (MgSO₄) and evaporated. The residue was triturated with ethyl acetate and the solid collected by filtration. Yield 1.4g.

25 ¹H NMR δ (DMSO) 12.05 (br s, 1H), 7.22 (t, 1H), 3.83 (d, 2H), 3.05-3.00 (m, 4H), 1.80-1.75 (m, 4H), 1.40 (s, 9H).

ii) 2-Amino-*N*-[(1*H*)-tetrazol-5-yl]acetamide

The product of step (i) (1.4g) was slurried in ethyl acetate, washed with 1N HCl and filtered. The filtrate was washed with water, dried (MgSO₄) and evaporated. The residue
30 was dissolved in dichloromethane (50ml) and trifluoroacetic acid (8ml) and stirred at room temperature for 2 hours. The mixture was evaporated. The residue was azeotroped with toluene and triturated with isohexane. The product was collected by filtration. Yield 0.45g.

¹H NMR δ (DMSO) 12.50 (br s, 1H), 8.24 (br s, 3H), 3.92 (br s, 2H)

iii) (\pm)-2-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]-*N*-[(1*H*)-tetrazol-5-yl]acetamide

The title compound was prepared from the product of step (ii) and the product of example 15 step (viii) by the method of example 7 step (i).

5 MS: APCI (+ve) 563 (M+1, 100%)

¹H NMR δ (DMSO, 90°C) 11.80 (br s, 1H), 11.21 (br s, 1H), 8.30 (d, 1H), 7.62 (s, 1H), 7.42-7.37 (m, 2H), 7.27 (br s, 1H), 7.19-7.11 (m, 5H), 6.91 (br s, 2H), 5.32 (s, 1H), 4.24 (d, 2H), 2.55 (q, 2H), 2.24 (s, 3H), 1.14 (t, 3H)

MP: 220-225°C

10

Example 46

(\pm)-*N*-[4-[5-{2-Ethyl-8-hydroxy-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-3-azetidinecarboxylic acid

15 **i) 2-(4-Ethylphenyl)-4,5-dihydro-4,4-dimethyloxazole**

The subtitle compound was prepared from 4-ethyl benzoic acid by the method of example 15 step (iii).

MS: APCI (+ve) 204 (M+1, 100%)

20 **ii) 2-(4-Ethyl-2-methylphenyl)-4,5-dihydro-4,4-dimethyloxazole**

To a solution of the product from step (i) (43g) in tetrahydrofuran (600ml) at -10°C was added *n*-butyllithium (2.5M solution in hexanes, 94ml). The mixture was stirred for 2.5 hours at 0°C then cooled to -30°C and treated with methyl iodide (62ml). The mixture was warmed to room temperature and partitioned between ethyl acetate and water. The organic

25 phase was dried and evaporated and the residue purified by chromatography eluting with 5% ethyl acetate in isohexane. Yield 28.4g.

MS: APCI (+ve) 218 (M+1, 100%)

30 **iii) 2-[2-[2-[3-Methoxyphenyl]ethyl]-4-methylphenyl]-4,5-dihydro-4,4-dimethyloxazole**

The subtitle compound was prepared from the product of step (ii) by the method of example 15 step (iv).

MS: APCI (+ve) 338 (M+1, 100%)

iv) 2-[2-[3-Methoxyphenyl]ethyl]-4-methylbenzoic acid

The subtitle compound was prepared from the product of step (iii) by the method of example 15 step (v).

MS: APCI (-ve) 283 (M-1,100%)

5

v) 2-Ethyl-10,11-dihydro-8-methoxy-5H-dibenzo[*a,d*]cyclohepten-5-one

The subtitle compound was prepared from the product of step (iv) by the method of example 15 step (vi).

MS: APCI (+ve) 267 (M+1,100%)

10

vi) (±)-5-[2-Ethyl-8-methoxy-5H-dibenzo[*a,d*]cyclohepten-5-yl]-2,4(1*H*,3*H*)-pyrimidinedione

The subtitle compound was prepared from the product of step (v) by the method of example 8 step (i).

MS: APCI (+ve) 361 (M+1,100%)

15

vii) (±)-5-[2-Ethyl-8-[(1,1-dimethylethyl)dimethylsilyloxy]-5H-dibenzo[*a,d*]cyclohepten-5-yl]-2,4(1*H*,3*H*)-pyrimidinedione

A mixture of the product from step (vi) (7.1g) and boron tribromide (1.0M solution in dichloromethane, 40ml) in dichloromethane (30ml) was stirred at room temperature for 4 hours then partitioned between ethyl acetate and 2M HCl. The organic phase was washed with water, dried (MgSO₄) and evaporated. The residue was dissolved in dimethylformamide (50ml) and *tert*-butyldimethylsilyl chloride (4.52g) and imidazole (3.4g) were added. The reaction mixture was stirred at room temperature overnight and partitioned between ethyl acetate and water. The organic phase was washed with water, dried (MgSO₄) and evaporated. The residue was purified by chromatography eluting with 40-60% ethyl acetate in isohexane. Yield 5.23g.

20
25

MS: APCI (+ve) 461 (M+1,100%)

viii) 1-[2-Chloropyrimidin-4-yl]-5-[2-ethyl-8-[(1,1-dimethylethyl)dimethylsilyloxy]-5H-dibenzo[*a,d*]cyclohepten-5-yl]-2,4(1*H*,3*H*)-pyrimidinedione

The subtitle compound was prepared from the product of step (vii) by the method of example 1 step (v).

MS: APCI (+ve) 573 (M+1,100%)

35

ix) $(\pm)2$ -[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]-*N*-[(1*H*)-tetrazol-5-yl]acetamide

A mixture of the product from step (viii) (0.5g), 3-carboxyazetidine (0.13g) and *N,N*-diisopropylethylamine (0.52ml) in 1-methyl-2-pyrrolidinone (10ml) was heated at 90°C for 6 hours and partitioned between ethyl acetate and 1M HCl. The organic phase was washed with water, dried (MgSO₄) and concentrated *in vacuo* to 10ml. Isohexane (5ml) was added and the product was collected by filtration. Yield 0.25g.

MS: APCI (+ve) 524 (M+1, 100%)

¹H NMR δ (DMSO, 90°C) δ 12.42 (br s, 1H), 11.18 (s, 1H), 9.10 (s, 1H), 8.31 (d, 1H), 7.82 (s, 1H), 7.39 (d, 1H), 7.33-7.29 (m, 2H), 7.21-7.18 (m, 2H), 6.89-6.71 (m, 4H), 5.25 (s, 1H), 4.22-4.14 (m, 2H), 4.06-4.03 (m, 2H), 3.57-3.52 (m, 1H), 2.60 (q, 2H), 1.17 (t, 3H).

MP: 220°C

Example 47

$(\pm)2$ -[[[4-[5-{2-Ethyl-8-hydroxy-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid

i) $(\pm)2$ -[[[4-[5-{2-Ethyl-8-[(1,1-dimethylethyl)dimethylsilyloxy]-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid, ethyl ester

The subtitle compound was prepared from the product of example 46 step (viii) and the product of example 10 step (i) by the method of example 7 step (i), with an acid wash (1M HCl) during work-up.

MS: APCI (+ve) 666 (M+1, 100%)

ii) $(\pm)2$ -[[[4-[5-{2-Ethyl-8-hydroxy-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid

The title compound was prepared from the product of step (i) by the method of example 1 step (vii).

MS: APCI (+ve) 638 (M+1, 100%)

¹H NMR δ (DMSO, 90°C) δ 12.00 (br s, 1H), 11.19 (s, 1H), 8.29 (d, 1H), 7.62 (s, 1H), 7.38 (d, 1H), 7.29 (d, 1H), 7.24 (br s, 1H), 7.17-7.10 (m, 3H), 6.95 (s, 1H), 6.91-6.75 (m, 4H), 5.25 (s, 1H), 4.28-4.17 (m, 2H), 3.61 (s, 2H), 2.52 (q, 2H), 1.13 (t, 3H).

MP: 225 °C

Example 48

(±) 2-[5-{2-Ethyl-8-methyl-5H-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-N-[(1*H*)-tetrazol-5-ylamino]carboxymethyl]-4-pyrimidinecarboxamide

- 5 A stirred solution of the product from example 41 step (v) (0.42g), the product from example 45 step (ii) (0.345g), *N,N*-diisopropylethylamine (0.7ml) and bromo-tris(pyrrolidino)-phosphonium hexafluorophosphate (0.632g) in dry *N,N*-dimethylformamide (10ml) was treated with *N,N*-dimethyl-4-aminopyridine (0.111g). After 96 hours the mixture was partitioned between 1*N* hydrochloric acid and ethyl acetate.
- 10 The organic layer was washed with water, dried (MgSO₄) and concentrated to low volume. Addition of isohexane gave a solid which was purified by C18 reverse phase chromatography eluting with 50% to 80% methanol in 0.1% aqueous ammonium acetate solution. Yield 0.044g
- MS:APCI (-ve) 589 (M-1, 100%)
- 15 ¹H NMR δ (DMSO) 15.94 (br s, 1H), 12.20 (br s, 1H), 11.55 (s, 1H), 9.14 (d, 1H), 9.05 (t, 1H), 8.03 (d, 1H), 7.44 (dd, 2H), 7.19 (m, 4H), 6.92 (dd, 2H), 5.35 (s, 1H), 4.26 (d, 2H), 2.56 (q, 2H), 2.26 (s, 3H), 1.17 (t, 3H)
- MP: 215-220 °C dec.

20 **Example 49**

(±)-4-[Carboxymethylamino]-2-[5-[2-ethyl-8-methyl-5H-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-2*H*-pyrimidin-1-yl]-5-pyrimidinecarboxylic acid

- i) (±)-4-[[1,1-Dimethylethoxycarbonyl]methylamino]-2-[5-[2-ethyl-8-methyl-5H-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-2*H*-pyrimidin-1-yl]-5-pyrimidinecarboxylic acid, methyl ester
- 25

The subtitle compound was prepared from the products of example 17 step (ii) and example 15 step (vii) by the method of example 17 step (iii).

- 30 MS:APCI(+ve) 610 (M+1, 100%)

ii) (±)-4-[Carboxymethylamino]-2-[5-[2-ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-2*H*-pyrimidin-1-yl]-5-pyrimidinecarboxylic acid

The title compound was prepared from the product of step (i) by the method of example 1 step (vii).

MS: APCI(+ve) 540 (M+1, 100%)

¹H NMR δ (DMSO) 13.65 (br s, 1H), 13.00 (br s, 1H), 11.83 (t, 1H), 11.38 (s, 1H), 7.46-7.40 (m, 2H), 7.23-7.17 (m, 5H), 6.92 (s, 2H), 5.32 (s, 1H), 4.16 (d, 2H), 2.58 (q, 2H), 2.28 (s, 3H), 1.16 (t, 3H).

MP: >200°C (decomp.)

Example 50

5-[2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidine

The title compound was prepared from the product of example 8 step (i) (4g) by the method of example 1 step (vi). Yield 0.5g

MS: APCI (+ve): 347 (M+1, 100%), APCI (-ve): 345 (M-1, 100%)

¹H NMR δ (DMSO) 12.33 (s, 1H), 11.19 (br s, 1H), 7.54 (d, 2H), 7.20(s+d, 4H), 6.9 (s, 2H), 6.74 (s, 1H), 5.82 (s, 1H), 2.30 (s, 6H)

MP: 287 °C

Example 51

5-[2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-1-methyl-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidine

i) 10,11-Dihydro-2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-ol

Diisobutylaluminium hydride (5.5ml of a 1M solution in tetrahydrofuran) was added dropwise to 10,11-dihydro-2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-one (European Patent, 1993, 0 589 322 A1) (1.2g) in tetrahydrofuran (20ml) at -78 °C. After 1 hour the cooling bath was removed and the reaction was stirred at r.t. for 2 hours. The reaction was quenched with brine and methanol. After 0.5 hours the reaction was partitioned between ethyl acetate and water. The ethyl acetate solution was washed with water, brine, dried (MgSO₄) and evaporated. Purification was by chromatography eluting with toluene. Yield 1.2g. Used directly in step (ii)

ii) 5-(2,8-Dimethyl-5H-dibenzo[a,d]cyclohepten-5-yl)-1-methyl-2,4(3H)-pyrimidinedione

To a solution of the product of step (i) (0.094 g) in trifluoroacetic acid (4 ml) under a nitrogen atmosphere was added 1-methyluracil (0.01 g), and the mixture stirred at room temperature for 1 hour. Evaporation of solvent afforded an orange oil which was azeotroped once with acetonitrile (5 ml). The crude product was redissolved in acetonitrile (2 ml), and stirred at room temperature for 0.5 h, giving a white precipitate. The reaction mixture was diluted with water (10 ml) and the white precipitate isolated by filtration. Yield: 0.085g

MS: APCI(+ve) 345 (M+1, 100%)

¹H NMR δ (CDCl₃) 7.83 (br s, 1H), 7.40 (d, 2H), 7.18 (d, 2H), 7.13 (s, 2H), 6.83 (s, 2H), 6.56 (s, 1H), 5.29 (s, 1H), 3.18 (s, 3H), 2.33 (s, 6H).

MP: 260°C

15

iii) 5-[2,8-Dimethyl-5H-dibenzo[a,d]cyclohepten-5-yl]-1-methyl-3,4-dihydro-2-oxo-4-thioxo-1(2H)-pyrimidine

The title product was prepared from the product of step (ii) (0.14g) by the method of example 1 step (vi). Purification was by chromatography eluting with 30% ethyl acetate in isohexane. Yield: 0.10g

MS: APCI(+ve) 361 (M+1, 100%)

¹H NMR δ (CDCl₃) 9.27 (br s, 1H), 7.52 (d, 2H), 7.17 (d, 2H), 7.13 (s, 2H), 6.93 (s, 1H), 6.85 (s, 2H), 5.83 (s, 1H), 3.22 (s, 3H), 2.33 (s, 6H).

MP: 275°C

25

PHARMACOLOGICAL DATA

The following example describes the assay used to determine how strongly the compounds of the invention bind to P2-purinoceptor 7-TM G-protein coupled receptors. The assay used a human P2Y2 receptor clone which was isolated from HL60 cells cDNA and then stably transfected into a Jurkat cell line (using methods described in "Cloning and Characterisation of a Bovine P_{2Y} Receptor" Henderson *et al* (1995), 212, 2, 648-656; Parr *et al* Proc. Natl. Acad. Sci USA (1994), 91, 3275-3279 and Proc Natl Acad Sci USA (1994), 91, 13067). The cloned receptor mediates an increase in intracellular calcium in the cell line, which possesses no endogenous nucleotide receptor of its own.

The transfected Jurkat cells were maintained at a concentration of from about 1×10^5 to 10×10^5 cells/ml in RPMI containing 4% heat inactivated bovine serum, 2% penicillin/streptomycin and 1% glutamine. The cells were incubated at 37°C in an atmosphere of air with 5% CO₂.

The cells were spun down at 1000 r.p.m. for 5 minutes and resuspended in 10ml basal salt solution (BSS) containing 125 mM of NaCl, 5 mM of KCl, 1 mM of MgCl, 1.5 mM of CaCl₂, 25 mM of HEPES, 5 mM of glucose and 1 mg/ml of bovine serum albumin, having a pH of 7.3. The concentration of cells was determined using a Technicon cell counter. From 0.75×10^8 to 1×10^8 cells were spun down, resuspended to a concentration of 3.3×10^7 cells/ml in BSS and incubated with either 17 μ M fluo-3AM or 17 μ M Fura-2AM at 37°C for 35 minutes with vigorous shaking. The dye used was dependent upon the fluorescence and absorption properties of the compounds of the invention. In general for compounds of formula (I) wherein Q¹ represents a S atom, fluo-3AM was used and for compounds wherein Q¹ represents an O atom, either fluo-3AM or fura-2AM were used. The cells were again spun down and washed once with the same volume of BSS before being resuspended in BSS to a concentration of 1×10^6 cells/ml ready for testing.

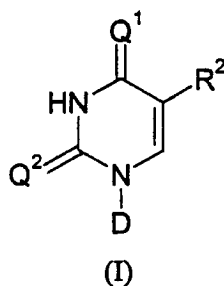
When fluo-3AM was used as the dye, the cell solution was left at room temperature to recover for approximately 30 minutes before testing.

Fura-2AM loaded cells were divided into aliquots of about 10 ml and were warmed to 37°C for 10 minutes before testing.

- Calcium responses were measured on a SPEX Fluomax using 508 nm excitation and 525 nm emission wavelengths at room temperature for Fluo-3AM loaded cells and 340/380 nm excitation and 510 nm emission wavelengths for Fura-2AM loaded cells. Each cuvette contained 2 ml of cells and was stirred at high speed throughout the test. Basal
- 5 fluorescence was measured for 5 seconds before 20 μ l of a 10^{-2} - 10^{-6} M solution of the test compound in water was added to the 2ml solution of the cells. The response was calibrated by the addition of Triton-X-100 (68 μ l, 10% solution) and then EGTA (180 μ l, 0.5 M solution). For each compound the response was compared to that of UTP.
- 10 The compounds exemplified have pA2 values greater than 4.0.

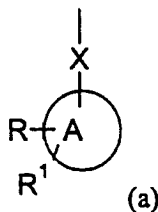
Claims

1. A compound of formula I:



in which:

D is hydrogen, C₁₋₆alkyl or a group of formula (a):



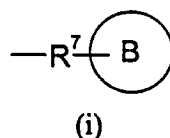
where A is a 6-membered heterocyclic ring containing 1 to 3 nitrogen atoms or a fused 5,6-bicyclic ring containing 1 to 4 nitrogen atoms;

X is a bond or CH₂ group;

R is hydrogen, NO₂, NH₂, N(C₁₋₆alkyl)₂, CO₂H, CO₂C₁₋₆alkyl, phenyl substituted by CH₂CO₂H, or CONR³R⁴ where R³ and R⁴ are independently hydrogen, C₁₋₆alkyl optionally substituted by hydroxy and/or optionally interrupted by oxygen, nitrogen or sulfur;

R¹ is -R⁵-tetrazol-5-yl where R⁵ is a bond, OCH₂, SCH₂, CONH, CONHCH₂,

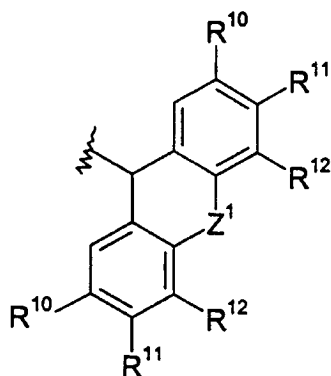
CONHCH₂CONH, NHCH₂CONH, NHCH(R³) or -R⁵-CO₂H where R⁵ is a bond, OCH₂, SCH₂, CONHCH₂ or NHCH(R³) where R³ is as defined above or R⁵ is NR⁶(CH₂)_q where R⁶ is hydrogen or C₁₋₆alkyl and q is 1 or 2, or R¹ is a group of formula (i):



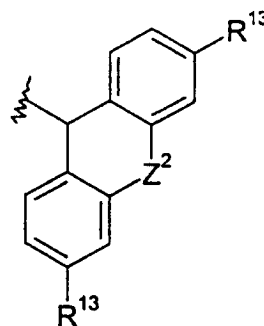
where B is a 4-, 5-, or 6-membered saturated ring containing a nitrogen atom optionally substituted by hydroxy and substituted by CO_2H or CONH-Het where Het is tetrazol-5-yl, or a thiazole or thiadiazole ring substituted by $\text{CH}_2\text{CO}_2\text{H}$, or B is a 5-membered aromatic heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur optionally substituted by CF_3 , CO_2H , $\text{CH}_2\text{CO}_2\text{H}$, $\text{C}(\text{CO}_2\text{H})=\text{N-OMe}$, tetrazol-5-yl or $\text{CH}_2\text{tetrazol-5-yl}$; and

R^7 is a bond, sulfur atom, a group $-\text{NR}^8-\text{CH}(\text{CO}_2\text{H})-\text{CH}_2-$, or a group $-\text{CONR}^8(\text{CH}_2)_p\text{CONR}^9-$ or $-\text{NR}^8-(\text{CH}_2)_p\text{CONR}^9-$ where R^8 and R^9 are independently hydrogen or $\text{C}_{1-6}\text{alkyl}$ and p is 1 or 2;

R^2 is a group of formula (ii) or (iii):



(ii)



(iii)

15

where R^{10} groups are independently hydrogen, halogen, methoxy, methylthio or $\text{C}_{1-3}\text{alkyl}$ (optionally substituted by one or more fluorine atoms);

R^{11} groups are independently hydrogen, halogen, hydroxy, $\text{C}_{1-3}\text{alkylthio}$, $\text{C}_{1-4}\text{alkyl}$ (optionally substituted by one or more fluorine atoms), $\text{C}_{3-4}\text{cycloalkyl}$, MeOCH_2 , MeSCH_2 or $\text{C}_{1-2}\text{alkoxy}$;

20

R^{12} groups are independently hydrogen, halogen or methyl (optionally substituted by one or more fluorine atoms);

Z^1 is $\text{CH}=\text{CH}$, $\text{CF}=\text{CH}$ or $\text{CF}=\text{CF}$;

Z^2 is a single bond, oxygen, sulphur, $\text{CH}_2\text{CH}=\text{CH}$, $\text{CH}_2\text{CH}=\text{CHCH}_2$ or a $\text{C}_{1-4}\text{alkylene}$ group optionally interrupted by an oxygen or sulphur atom;

25

R^{13} are independently hydrogen, halogen, $\text{C}_{1-3}\text{alkyl}$, CF_3 , or a methylthio group or hydroxy;

Q^1 and Q^2 each independently represent an O or S;

provided that when Q^1 is oxygen, R^2 is a group of formula (ii).

2. A compound according to claim 1 in which D is hydrogen or C₁₋₆alkyl
3. A compound according to claim 1 or 2 in which D is a group of formula (a) where A is
5 pyridine or pyrimidine.
4. A compound according to any one of claims 1 to 3 in which R is hydrogen.
5. A compound according to any one of claims 1 to 4 in which R¹ is a group
10 -R⁵-CO₂H, where R⁵ is SCH₂, NHCH₂ or NMeCH₂
6. A compound according to any one of claims 1 to 5 in which R⁷ is a bond and B is a
4- or 5-membered saturated ring containing a nitrogen atom substituted by CO₂H and
optionally substituted by hydroxy.
- 15 7. A compound according to any one of claims 1 to 6 in which B is a 5-membered
aromatic heterocycle and R⁷ is a group -NR⁸-(CH₂)_p-CONR⁹-.
8. A compound according to any one of claims 1 to 6 in which B is thiazole or thiadiazole
20 substituted by CO₂H or CH₂CO₂H.
9. A compound according to any one of claims 1 to 8 in which Q¹ is S or O and Q² is O.
10. A compound according to claim 1 which is:
 - 25 6-[[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-
pyrimidinyl]methyl]-2-pyridinecarboxylic acid
 - 2-[[6-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-
pyrimidinyl]pyridazin-3-yl]thio]acetic acid
 - 5-[5*H*-Dibenzo[*a,d*]cyclohepten-5-yl]-1-[6-[[5-[trifluoromethyl]-1,2,4-triazol-3-
30 yl]thio]pyridazin-3-yl]-2,4(1*H*,3*H*)-pyrimidinedione
 - 5-[5*H*-Dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-4-thioxo-1-[6-[[5-[trifluoromethyl]-
1,2,4-triazol-3-yl]thio]pyridazin-3-yl]-2(1*H*)-pyrimidinone
 - 4-[2-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-
pyrimidinyl]-4-[carboxymethylthio]pyrimidin-5-yl]phenylacetic acid
 - 35 2-[[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-
pyrimidinyl]pyrimidin-2-yl]thio]acetic acid

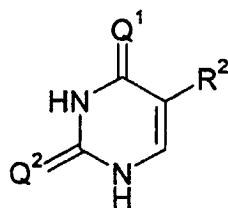
- N*-[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine
- N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine
- 5 *N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]glycine
- 2-[2-[[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid
- N*-[4-[5-{5*H*-Dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline
- 10 *N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline
- (2*S-trans*)-*N*-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-4-hydroxy-2-pyrrolidinecarboxylic acid
- 15 *N*^α-[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-histidine
- (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid
- 2-[2-[[2-[Dimethylamino]-4-[5-{2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-6-yl]amino]acetyl]amino]-4-thiazoleacetic acid
- 20 acid
- N*-[2-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-5-[methoxycarbonyl]pyrimidin-4-yl]glycine
- 4-[[Carboxymethyl]amino]-2-[5-{2,8-dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-5-pyrimidinecarboxylic acid
- 25 (±)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*N*-methylglycine
- (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid
- 30 acid
- 2-[2-[[4-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid
- (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid
- 35 acid

- (±)-2-[2-[[4-[3,4-Dihydro-5-{2-methoxy-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid
- (±)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-3-azetidinecarboxylic acid
- 2-[2-[[6-[5-{2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-4-yl][methyl]amino]acetyl]amino]-4-thiazoleacetic acid
- (±)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline
- (±)-*N*-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-L-proline
- (±)-2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-9*H*-purine-9-acetic acid.
- N*-[2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-5-nitropyrimidin-4-yl]glycine.
- (±)-2-[2-[[4-[3,4-dihydro-5-{2-methyl-8-[1-methylethyl]-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid
- (±)-2-[2-[[4-[3,4-Dihydro-5-{2-methyl-8-propyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid
- (±)-*N*-[4-[3,4-Dihydro-5-{2-methyl-8-propyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2-oxo-4-thioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-*N*-methylglycine
- (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-5-thiazoleacetic acid
- (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-4-thiazolecarboxylic acid.
- (±)-2-[[1-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]azetidin-3-yl]carbonylamino]-4-thiazoleacetic acid
- (±)-2-[2-[[4-[3,4-Dihydro-5-{2-hydroxy-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid.
- (±)-2-[2-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl][methyl]amino]acetyl]amino]-α-[methoxyimino]-4-thiazoleacetic acid

- (±)-*N*-[(1*H*)-Tetrazol-5-yl]-1-[4-[5-{2-ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-3-azetidinecarboxamide
- (±)-2-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino-*N*-[4-[1*H*-tetrazol-5-ylmethyl]thiazol-2-yl]acetamide
- (±)[[5-[[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-3-(1,2,4-thiadiazole)]acetic acid
- (±)2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-4-pyrimidinecarboxylic acid
- (±)*N*-[[[2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-4-yl]carbonyl]glycine
- (±)2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-*N*-[(1*H*)-tetrazol-5-yl]-4-pyrimidinecarboxamide
- (±)2-[[6-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyridazin-3-yl]thio]acetic acid
- (±)2-[4-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]-*N*-[(1*H*)-tetrazol-5-yl]acetamide
- (±)*N*-[4-[5-{2-Ethyl-8-hydroxy-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]-3-azetidinecarboxylic acid
- (±)2-[[[4-[5-{2-Ethyl-8-hydroxy-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]pyrimidin-2-yl]amino]acetyl]amino]-4-thiazoleacetic acid
- (±)2-[5-{2-Ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl}-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-*N*-[[(1*H*)-tetrazol-5-ylamino]carboxymethyl]-4-pyrimidinecarboxamide
- (±)-4-[Carboxymethylamino]-2-[5-[2-ethyl-8-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2,4-dioxo-2*H*-pyrimidin-1-yl]-5-pyrimidinecarboxylic acid
- 5-[2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidine
- 5-[2,8-Dimethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-yl]-1-methyl-3,4-dihydro-2-oxo-4-thioxo-1(2*H*)-pyrimidine
- or salts thereof.

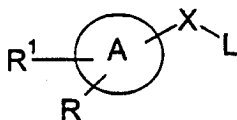
11. A compound according to any one of claims 1 to 10 for use in therapy.

12. A pharmaceutical composition comprising a compound of formula I or a salt or solvate thereof as defined in any one of claims 1 to 8 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.
13. A process for the preparation of compounds of formula I which comprises:
- (a) reacting a compound of formula (II):



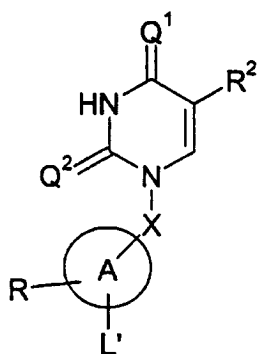
(II)

where Q^1 and Q^2 are as defined in formula (I) and R^2 is as defined in formula (I) or are protected derivatives thereof with a compound of formula (III):



(III)

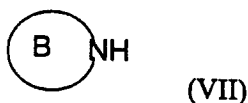
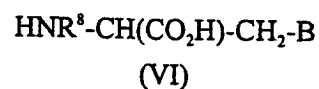
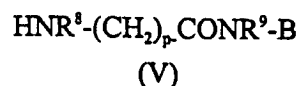
- where R , R^1 and A are as defined in formula (I) or are protected derivatives thereof, X is as defined in formula (I) and L is a leaving group, or
- (b) reacting a compound of formula (IV):



(IV)

where Q^1 , Q^2 and X are as defined in formula (I), R and A are as defined in formula (I) or are protected derivatives thereof and L' is a leaving group with a compound of formula (V), (VI) or (VII):

5



10

where R^8 , R^9 and p are as defined in formula (I) and B is as defined in formula (I) or is a protected derivative thereof, or

(c) when R^1 is a group $-\text{R}^5\text{-CO}_2\text{H}$ and R^5 is SCH_2 or $\text{NR}^6(\text{CH}_2)_q$, reacting a compound of formula (iv) as defined above with a compound $\text{H-R}^5\text{-CO}_2\text{R}^{14}$ where R^5 is SCH_2 or

15

$\text{NR}^6(\text{CH}_2)_q$ and R^{14} is an ester forming group;

and optionally thereafter (a), (b) or (c) in any order:

- removing any protecting groups
- converting the compound of formula (I) into a further compound of formula (I)
- forming a salt.

20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01240

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 239/46, C07D 403/04, C07D 403/06, C07D 403/14, C07D 401/04,
C07D 401/06, C07D 413/14, A61K 31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

9 October 1998

Date of mailing of the international search report

01 -11- 1998

Name and mailing address of the ISA/

Swedish Patent Office

Box 5055, S-102 42 STOCKHOLM

Facsimile No. +46 8 666 02 86

Authorized officer

Göran Karlsson

Telephone No. +46 8 782 25 00